CBDA Literature

Medical cannabis in the UK: From principle to practice.

Schlag, Anne Katrin [1]; Baldwin, David S [2] ; Barnes, Michael [3] ; Bazire, Steve [4] ; Coathup, Rachel [5] ; Curran, H Valerie [6] ; McShane, Rupert [7] ; Phillips, Lawrence D [8] ; Singh, Ilina [9] ; Nutt, David J [10] [1] Drug Science, London, UK. [2] Clinical and Experimental Sciences, University of Southampton, Southampton, UK. [3] University of Newcastle, Newcastle upon Tyne, UK. [4] School of Pharmacy, University of East Anglia, Norwich, UK. [5] University of Manchester, Manchester, UK. [6] Clinical, Education and Health Psychology, University College London, London, UK. [7] Interventional Psychiatry Service, Oxford Health NHS Foundation Trust, Oxford, UK. [8] Department of Management, London School of Economics &Political Science, London, UK. [9] Department of Psychiatry, University of Oxford, Oxford, UK. [10] Department of Brain Sciences, Imperial College London, London, UK. .

Journal of psychopharmacology (Oxford, England) Vol. 34, Iss. 9, (September 2020): 931-937.

ABSTRACT

BACKGROUND

In the UK, medical cannabis was approved in November 2018, leading many patients to believe that the medicine would now be available on the NHS. Yet, to date, there have been only 12 NHS prescriptions and less than 60 prescriptions in total. In marked contrast, a recent patient survey by the Centre for Medical Cannabis (Couch, 2020) found 1.4 m people are using illicit cannabis for medical problems.

AIMS

Such a mismatch between demand and supply is rare in medicine. This article outlines some of the current controversies about medical cannabis that underpin this disparity, beginning by contrasting current medical evidence from research studies with patient-reported outcomes.

OUTCOMES

Although definite scientific evidence is scarce for most conditions, there is significant patient demand for access to medical cannabis. This disparity poses a challenge for prescribers, and there are many concerns of physicians when deciding if, and how, to prescribe medical cannabis which still need to be addressed. Potential solutions are outlined as to how the medical profession and regulators could respond to the strong demand from patients and families for access to medical cannabis to treat chronic illnesses when there is often a limited scientific evidence base on whether and how to use it in many of these conditions.

CONCLUSIONS

There is a need to maximise both clinical research and patient benefit, in a safe, cautious and ethical manner, so that those patients for whom cannabis is shown to be effective can access it. We hope our discussion and outlines for future progress offer a contribution to this process.

DETAILS

Correspondence author:	Schlag, Anne Katrin
Publication title:	Journal of psychopharmacology (Oxford, England)
Journal abbreviation:	J. Psychopharmacol. (Oxford)
Volume:	34

Issue:	9
Pages:	931-937
Number of pages:	7
Publication year:	2020
Country of publication:	United States
ProQuest document ID:	2412218044
Document URL:	https://search.proquest.com/docview/2412218044?accountid=47765

Cannabidiolic Acid, a Still Overlooked Bioactive Compound: An Introductory Review and Preliminary Research.

Formato, Marialuisa [1] ; Crescente, Giuseppina [1] ; Scognamiglio, Monica [1] ; Fiorentino, Antonio [1] ; Pecoraro, Maria Tommasina [1] ; Piccolella, Simona [1] ; Catauro, Michelina [2] ; Pacifico, Severina [1] [1] Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "Luigi Vanvitelli", Via Vivaldi 43, 81100 Caserta, Italy. [2] Department of Engineering, University of Campania "Luigi Vanvitelli", Via Roma 29, I-81031 Aversa, Italy.

Molecules (Basel, Switzerland) Vol. 25, Iss. 11, (June 5, 2020).

ABSTRACT

Cannabidiolic acid (CBDA) is the main phytocannabinoid in fiber and seed-oil hemp (Cannabis sativa L.) plants, but its potential health-related capabilities have been masked for years by a greater scientific interest towards its neutral derivative cannabidiol (CBD). This review aims to collect from the literature and critically discuss all the information about this molecule, starting from its biosynthesis, and focusing on its bioactivity, as an anti-inflammatory, anti-emetic, anti-convulsant, and anti-cancerogenic drug. Furthermore, in the awareness that, despite its multiple bioactive effects, currently poor efforts have been made to achieve its reliable purification, herein, we propose a relatively simple, fast, and inexpensive procedure for its recovery from pollen of industrial hemp cultivars. Spectroscopic and spectrometric techniques allowed us to unequivocally identify pure isolated CBDA and to distinguish it from the constitutional isomer tetrahydrocannabinolic acid (THCA-A).

DETAILS

Correspondence author:	Formato, Marialuisa
Publication title:	Molecules (Basel, S witzerland)
Journal abbreviation:	Molecules
Volume:	25
Issue:	11
Publication year:	2020
Country of publication:	Switzerland
ProQuest document ID:	2411553732
Document URL:	https://search.proquest.com/docview/2411553732?accountid=47765

Future Aspects for Cannabinoids in Breast Cancer Therapy.

Kisková, Terézia [1] ; Mungenast, Felicitas [2] ; Suváková, Mária [3] ; Jäger, Walter [4] ; Thalhammer, Theresia [5 1]
Institute of Biology and Ecology, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Šrobárova 2, 04154 Košice, Slovakia. terezia.kiskova@upjs.sk. [2] Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. felicitas.mungenast@meduniwien.ac.at. [3] Institute of Chemistry, Faculty of Sciences, University of Pavol Jozef Šafárik in Košice, Šrobárova 2, 04154 Košice, Slovakia. maria.suvakova@student.upjs.sk. [4] Department of Clinical Pharmacy and Diagnostics, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria. walter.jaeger@univie.ac.at. [5] Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. theresia.thalhammer@meduniwien.ac.at. .

International journal of molecular sciences Vol. 20, Iss. 7, (April 3, 2019).

ABSTRACT

Cannabinoids (CBs) from Cannabis sativa provide relief for tumor-associated symptoms (including nausea, anorexia, and neuropathic pain) in the palliative treatment of cancer patients. Additionally, they may decelerate tumor progression in breast cancer patients. Indeed, the psychoactive delta-9-tetrahydrocannabinol (THC), non-psychoactive cannabidiol (CBD) and other CBs inhibited disease progression in breast cancer models. The effects of CBs on signaling pathways in cancer cells are conferred via G-protein coupled CB-receptors (CB-Rs), CB1-R and CB2-R, but also via other receptors, and in a receptor-independent way. THC is a partial agonist for CB1-R and CB2-R; CBD is an inverse agonist for both. In breast cancer, CB1-R expression is moderate, but CB2-R expression is high, which is related to tumor aggressiveness. CBs block cell cycle progression and cell growth and induce cancer cell apoptosis by inhibiting constitutive active pro-oncogenic signaling pathways, such as the extracellular-signal-regulated kinase pathway. They reduce angiogenesis and tumor metastasis in animal breast cancer models. CBs are not only active against estrogen receptor-positive, but also against estrogen-resistant breast cancer cells. In human epidermal growth factor receptor 2-positive and triple-negative breast cancer cells, blocking protein kinase B- and cyclooxygenase-2 signaling via CB2-R prevents tumor progression and metastasis. Furthermore, selective estrogen receptor modulators (SERMs), including tamoxifen, bind to CB-Rs; this process may contribute to the growth inhibitory effect of SERMs in cancer cells lacking the estrogen receptor. In summary, CBs are already administered to breast cancer patients at advanced stages of the disease, but they might also be effective at earlier stages to decelerate tumor progression.

DETAILS

Correspondence author:	Kisková, Terézia
Publication title:	International journal of molecular sciences
Journal abbreviation:	Int J Mol Sci
Volume:	20
Issue:	7
Publication year:	2019
Country of publication:	Switzerland

Effect of cannabidiolic acid and ∆9-tetrahydrocannabinol on carrageenan-induced hyperalgesia and edema in a rodent model of inflammatory pain.

Rock, Erin M [1] ; Limebeer, Cheryl L [1] ; Parker, Linda A [2]

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Psychopharmacology Vol. 235, Iss. 11, (November 2018): 3259-3271.

ABSTRACT

RATIONALE

Cannabidiol (CBD), a non-intoxicating component of cannabis, or the psychoactive Δ9-tetrahydrocannabiol (THC), shows anti-hyperalgesia and anti-inflammatory properties.

OBJECTIVES

The present study evaluates the anti-inflammatory and anti-hyperalgesia effects of CBD's potent acidic precursor, cannabidiolic acid (CBDA), in a rodent model of carrageenan-induced acute inflammation in the rat hind paw, when administered systemically (intraperitoneal, i.p.) or orally before and/or after carrageenan. In addition, we assess the effects of oral administration of THC or CBDA, their mechanism of action, and the efficacy of combined ineffective doses of THC and CBDA in this model. Finally, we compare the efficacy of CBD and CBDA.

RESULTS

CBDA given i.p. 60 min prior to carrageenan (but not 60 min after carrageenan) produced dose-dependent anti-hyperalgesia and anti-inflammatory effects. In addition, THC or CBDA given by oral gavage 60 min prior to carrageenan produced anti-hyperalgesia effects, and THC reduced inflammation. The anti-hyperalgesia effects of THC were blocked by SR141716 (a cannabinoid 1 receptor antagonist), while CBDA's effects were blocked by AMG9810 (a transient receptor potential cation channel subfamily V member 1 antagonist). In comparison to CBDA, an equivalent low dose of CBD did not reduce hyperalgesia, suggesting that CBDA is more potent than CBD for this indication. Interestingly, when ineffective doses of CBDA or THC alone were combined, this combination produced an anti-hyperalgesia effect and reduced inflammation.

CONCLUSION

CBDA or THC alone, as well as very low doses of combined CBDA and THC, has anti-inflammatory and anti-hyperalgesia effects in this animal model of acute inflammation.

DETAILS

Correspondence author:	Rock, Erin M
Publication title:	Psychopharmacology
Volume:	235

Issue:	11
Pages:	3259-3271
Number of pages:	13
Publication year:	2018
Country of publication:	Germany
ProQuest document ID:	2109327902
Document URL:	https://search.proquest.com/docview/2109327902?accountid=47765

Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort.

Baron, Eric P [1] ; Lucas, Philippe [2] ; Eades, Joshua [2] ; Hogue, Olivia [3 1] Center for Neurological Restoration - Headache and Chronic Pain Medicine, Department of Neurology, Cleveland Clinic Neurological Institute, 10524 Euclid Avenue, C21, Cleveland, OH, 44195, USA. barone2@ccf.org. [2] Tilray, 1100 Maughan Rd, Nanaimo, BC, V9X 1J2, Canada. [3] Section of Biostatistics, Department of Quantitative Health Sciences, Cleveland Clinic Lerner Research Institute, 9500 Euclid Avenue, JJN3, Cleveland, OH, 44195, USA. .

The journal of headache and pain Vol. 19, Iss. 1, (May 24, 2018): 37.

ABSTRACT

BACKGROUND

Medicinal cannabis registries typically report pain as the most common reason for use. It would be clinically useful to identify patterns of cannabis treatment in migraine and headache, as compared to arthritis and chronic pain, and to analyze preferred cannabis strains, biochemical profiles, and prescription medication substitutions with cannabis.

METHODS

Via electronic survey in medicinal cannabis patients with headache, arthritis, and chronic pain, demographics and patterns of cannabis use including methods, frequency, quantity, preferred strains, cannabinoid and terpene profiles, and prescription substitutions were recorded. Cannabis use for migraine among headache patients was assessed via the ID Migraine™ questionnaire, a validated screen used to predict the probability of migraine.

RESULTS

Of 2032 patients, 21 illnesses were treated with cannabis. Pain syndromes accounted for 42.4% (n = 861) overall; chronic pain 29.4% (n = 598;), arthritis 9.3% (n = 188), and headache 3.7% (n = 75;). Across all 21 illnesses, headache was a symptom treated with cannabis in 24.9% (n = 505). These patients were given the ID Migraine™ questionnaire, with 68% (n = 343) giving 3 "Yes" responses, 20% (n = 102) giving 2 "Yes" responses (97% and 93% probability of migraine, respectively). Therefore, 88% (n = 445) of headache patients were treating probable migraine with cannabis. Hybrid strains were most preferred across all pain subtypes, with "OG Shark" the most preferred strain in the ID Migraine™ and headache groups. Many pain patients substituted prescription medications with cannabis (41.2-59.5%), most commonly opiates/opioids (40.5-72.8%). Prescription substitution in headache patients included opiates/opioids (43.4%), anti-depressant/anti-anxiety (39%), NSAIDs (21%), triptans (8.1%), anti-convulsants (7.7%), muscle relaxers (7%), ergots (0.4%).

CONCLUSIONS

Chronic pain was the most common reason for cannabis use, consistent with most registries. The majority of headache patients treating with cannabis were positive for migraine. Hybrid strains were preferred in ID Migraine™, headache, and most pain groups, with "OG Shark", a high THC (Δ9-tetrahydrocannabinol)/THCA (tetrahydrocannabinolic acid), low CBD (cannabidiol)/CBDA (cannabidiolic acid), strain with predominant terpenes β-caryophyllene and β-myrcene, most preferred in the headache and ID Migraine™ groups. This could reflect the potent analgesic, anti-inflammatory, and anti-emetic properties of THC, with anti-inflammatory and analgesic properties of β-caryophyllene and β-myrcene. Opiates/opioids were most commonly substituted with cannabis. Prospective studies are needed, but results may provide early insight into optimizing crossbred cannabis strains, synergistic biochemical profiles, dosing, and patterns of use in the treatment of headache, migraine, and chronic pain syndromes.

DETAILS

Correspondence author:	Baron, Eric P
Publication title:	The journal of headache and pain
Journal abbreviation:	J Headache Pain
Grant:	A $10 patient account credit was offered to each patient completing the online survey, funded by Tilray.
Volume:	19
Issue:	1
Pages:	37
Number of pages:	1
Publication year:	2018
Country of publication:	England
ProQuest document ID:	2045269457
Document URL:	https://search.proquest.com/docview/2045269457?accountid=47765

Cannabis sativa L. and Nonpsychoactive Cannabinoids: Their Chemistry and Role against Oxidative Stress, Inflammation, and Cancer.

Pellati, Federica [1]; Borgonetti, Vittoria [2] ; Brighenti, Virginia [1] ; Biagi, Marco [2] ; Benvenuti, Stefania [1] ; Corsi, Lorenzo [1] [1] Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Campi 103/287, 41125 Modena, Italy. [2] Department of Physical Sciences, Earth and Environment, University of Siena, Strada Laterina 8, 53100 Siena, Italy. .

BioMed research international Vol. 2018, (2018): 1691428.

ABSTRACT

In the last decades, a lot of attention has been paid to the compounds present in medicinal Cannabis sativa L., such as Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), and their effects on inflammation and cancer-related pain. The National Cancer Institute (NCI) currently recognizes medicinal C. sativa as an effective treatment for providing relief in a number of symptoms associated with cancer, including pain, loss of appetite, nausea and vomiting, and anxiety. Several studies have described CBD as a multitarget molecule, acting as an adaptogen, and as a modulator, in different ways, depending on the type and location of disequilibrium both in the brain and in the body, mainly interacting with specific receptor proteins CB1 and CB2. CBD is present in both medicinal and fibre-type C. sativa plants, but, unlike Δ9-THC, it is completely nonpsychoactive. Fibre-type C. sativa (hemp) differs from medicinal C. sativa, since it contains only few levels of Δ9-THC and high levels of CBD and related nonpsychoactive compounds. In recent years, a number of preclinical researches have been focused on the role of CBD as an anticancer molecule, suggesting CBD (and CBD-like molecules present in the hemp extract) as a possible candidate for future clinical trials. CBD has been found to possess antioxidant activity in many studies, thus suggesting a possible role in the prevention of both neurodegenerative and cardiovascular diseases. In animal models, CBD has been shown to inhibit the progression of several cancer types. Moreover, it has been found that coadministration of CBD and Δ9-THC, followed by radiation therapy, causes an increase of autophagy and apoptosis in cancer cells. In addition, CBD is able to inhibit cell proliferation and to increase apoptosis in different types of cancer models. These activities seem to involve also alternative pathways, such as the interactions with TRPV and GRP55 receptor complexes. Moreover, the finding that the acidic precursor of CBD (cannabidiolic acid, CBDA) is able to inhibit the migration of breast cancer cells and to downregulate the proto-oncogene c-fos and the cyclooxygenase-2 (COX-2) highlights the possibility that CBDA might act on a common pathway of inflammation and cancer mechanisms, which might be responsible for its anticancer activity. In the light of all these findings, in this review we explore the effects and the molecular mechanisms of CBD on inflammation and cancer processes, highlighting also the role of minor cannabinoids and noncannabinoids constituents of Δ9-THC deprived hemp.

DETAILS

Correspondence author:	Pellati, Federica
Publication title:	BioMed research international
Journal abbreviation:	Biomed Res Int
Volume:	2018
Pages:	1691428
Number of pages:	1

Publication year:	2018
Country of publication:	United States
ProQuest document ID:	2179319986
Document URL:	https://search.proquest.com/docview/2179319986?accountid=47765

Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.

Takeda, Shuso [1] ; Okajima, Shunsuke; Miyoshi, Hiroko; Yoshida, Kazutaka; Okamoto, Yoshiko; Okada, Tomoko; Amamoto, Toshiaki; Watanabe, Kazuhito; Omiecinski, Curtis J; Aramaki, Hironori [1] Department of Molecular Biology, Daiichi University of Pharmacy, 22-1 Tamagawa-cho, Minami-ku, Fukuoka 815-8511, Japan.

Toxicology letters Vol. 214, Iss. 3, (November 15, 2012): 314-319.

ABSTRACT

Cannabidiol (CBD), a major non-psychotropic constituent of fiber-type cannabis plant, has been reported to possess diverse biological activities, including anti-proliferative effect on cancer cells. Although CBD is obtained from non-enzymatic decarboxylation of its parent molecule, cannabidiolic acid (CBDA), few studies have investigated whether CBDA itself is biologically active. Results of the current investigation revealed that CBDA inhibits migration of the highly invasive MDA-MB-231 human breast cancer cells, apparently through a mechanism involving inhibition of cAMP-dependent protein kinase A, coupled with an activation of the small GTPase, RhoA. It is established that activation of the RhoA signaling pathway leads to inhibition of the mobility of various cancer cells, including MDA-MB-231 cells. The data presented in this report suggest for the first time that as an active component in the cannabis plant, CBDA offers potential therapeutic modality in the abrogation of cancer cell migration, including aggressive breast cancers.

DETAILS

Correspondence author:	Takeda, Shuso
Publication title:	Toxicology letters
Journal abbreviation:	Toxicol. Lett.
Grant:	R01 ES016358. United States.
Volume:	214
Issue:	3
Pages:	314-319
Number of pages:	6
Publication year:	2012
Country of publication:	Netherlands
ProQuest document ID:	1122609468
Document URL:	https://search.proquest.com/docview/1122609468?accountid=47765

Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (MOH)—a pilot study

Pellesi, Lanfranco; Licata, Manuela; Verri, Patrizia; Vandelli, Daniele; Palazzoli, Federica; et al.

European Journal of Clinical Pharmacology; Heidelberg Vol. 74, Iss. 11, (Nov 2018): 1427-1436. DOI:10.1007/s00228-018-2516-3

ABSTRACT

Purpose

The recent release of a medical cannabis strain has given a new impulse for the study of cannabis in Italy. The National Health Service advises to consume medical cannabis by vaporizing, in decoction or oil form. This is the first study that explores the pharmacokinetics and tolerability of a single oral dose of cannabis as decoction (200 ml) or in olive oil (1 ml), as a first step to improve the prescriptive recommendations.

Methods

This is a single-center, open-label, two-period crossover study designed to assess the pharmacokinetics and tolerability of oral cannabis administered to 13 patients with medication overuse headache (MOH). A liquid chromatography tandem-mass spectrometry (LC-MS/MS) method was conducted for the quantification of THC, CBD, 11-OH-THC, THC-COOH, THC-COOH-glucuronide, THCA-A, and CBDA. Blood pressure, heart rate, and a short list of symptoms by numerical rating scale (NRS) were assessed.

Results

Decoctions of cannabis showed high variability in cannabinoids content, compared to cannabis oil. For both preparations, THCA-A and CBDA were the most widely absorbed cannabinoids, while THC and CBD were less absorbed. The most important differences concern the bioavailability of THC, higher in oil (AUC0–24 7.44, 95% CI 5.19, 9.68) than in decoction (AUC0–24 3.34, 95% CI 2.07, 4.60), and the bioavailability of CBDA. No serious adverse events were reported.

Conclusions

Cannabis decoction and cannabis oil showed different pharmacokinetic properties, as well as distinct consequences on patients. This study was performed in a limited number of patients; future studies should be performed to investigate the clinical efficacy in larger populations.

Details

Author:

Pellesi, Lanfranco [1] ; Licata, Manuela [2] ; Verri, Patrizia [2] ; Vandelli, Daniele [2] ; Palazzoli, Federica [2] ; Marchesi, Filippo [2] ; Cainazzo, Maria Michela [1] ; Pini, Luigi Alberto [3] ; Guerzoni, Simona [1]

Publication title: European Journal of Clinical Pharmacology; Heidelberg

Volume: 74

Issue: 11

Pages: 1427-1436

Serum cannabidiol, tetrahydrocannabinol (THC), and their native acid derivatives after transdermal application of a low-THC Cannabis sativa extract in beagles.

Hannon, Mary Beth; Deabold, Kelly A; Talsma, Bryce N; Lyubimov, Alex; Iqbal, Asif; et al.

Journal of veterinary pharmacology and therapeutics Vol. 43, Iss. 5, (September 2020): 508-511. DOI:10.1111/jvp.12896

ABSTRACT

Cannabinoids hold promise for treating health problems related to inflammation and chronic pain in dogs, in particular cannabidiol (CBD), and its native acid derivative cannabidiolic acid (CBDA). Information regarding systemic delivery of cannabinoids through transdermal routes is sparse. The purpose of this study was to determine pharmacokinetics of transdermal administration of a low-THC Cannabis sativa extract in healthy dogs. Six purpose-bred research beagles were treated with a transdermal CBD-CBDA-rich extract, and serum concentrations of CBD, CBDA, tetrahydrocannabinol (THC), and its acid derivative tetrahydrocannabinolic acid (THCA) were examined prior to and at the end of weeks 1 and 2. A 4 mg/kg dose of total cannabinoids twice daily resulted in appx 10 ng/ml of CBD, 21-32 ng/ml of CBDA, trace amounts of THCA, and unquantifiable amounts of THC in serum at the end of weeks 1 and 2 of treatment. Results showed that CBDA and THCA were absorbed better systemically than CBD or THC.

DETAILS

Correspondence author: Hannon, Mary Beth

Publication title: Journal of veterinary pharmacology and therapeutics

Journal abbreviation: J. Vet. Pharmacol. Ther.

Volume: 43

Issue: 5

Pages: 508-511

Number of pages: 4

Publication year: 2020

Country of publication: England

ProQuest document ID: 2429784957

Document URL: https://search.proquest.com/docview/2429784957?accountid=47765

Isolation, Purification, and Antimicrobial Characterization of Cannabidiolic Acid and Cannabidiol from Cannabis sativa L.

Martinenghi, Laura Daniela; Jønsson, Rie; Lund, Torben; Jenssen, Håvard; National Library of Medicine.

Biomolecules Vol. 10, Iss. 6, (June 12, 2020). DOI:10.3390/biom10060900

ABSTRACT

The emergence of multi-drug resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) causes a major threat to public health due to its limited therapeutic options. There is an urgent need for the development of new effective antimicrobial agents and alternative strategies that are effective against resistant bacteria. The parallel legalization of cannabis and its products has fueled research into its many therapeutic avenues in many countries around the world. This study aimed at the development of a reliable method for the extraction, purification, characterization, and quantification of cannabidiolic acid (CBDA) and its decarboxylated form cannabidiol (CBD) present in the fiber type Cannabis sativa L. The two compounds were extracted by ethanol, purified on a C18 sep-pack column, and the extracts were analyzed by high performance liquid chromatography coupled with ultraviolet (UV)-vis and ESI-MS (electrospray ionization mass spectrometry) detection. The antimicrobial effect of CBDA and CBD was also evaluated. CBD displayed a substantial inhibitory effect on Gram-positive bacteria with minimal inhibitory concentrations ranging from 1 to 2 µg/mL. Time kill analysis and minimal bactericidal concentration revealed potential bactericidal activity of CBDA and CBD. While cannabinoids showed a significant antimicrobial effect on the Gram-positive S. aureus and Staphylococcus epidermidis, no activity was noticed on Gram-negative Escherichia coli and Pseudomonas aeruginosa. CBDA presented a two-fold lower antimicrobial activity than its decarboxylated form, suggesting that the antimicrobial pharmacophore of the analyzed cannabinoids falls in the ability for permeabilizing the bacterial cell membrane and acting as a detergent-like agent. A synergy test performed on MRSA with CBD and a range of antibiotics did not indicate a synergetic effect, but noteworthy no antagonist influence either. CBD and CBDA manifested low hemolytic activity on human red blood cells. Likewise, the safety of CBD toward human keratinocyte cells presents no toxicity at a concentration of up to seven-fold higher than the antibacterial minimal inhibitory concentration. Similarly, both CBD and CBDA are well tolerated by mammals, including humans, and conserve a safe value limits for blood-contacting drug development. Overall, CBD exhibited a strong antimicrobial effect against Gram-positive strains and could serve as an alternative drug for tackling MRSA.

DETAILS

Correspondence author: Martinenghi, Laura Daniela

Publication title: Biomolecules

Volume: 10

Issue: 6

Publication year: 2020

Country of publication: Switzerland

ProQuest document ID: 2414409567

Document URL: https://search.proquest.com/docview/2414409567?accountid=47765

Cannabis Therapeutics and the Future of Neurology

Russo, Ethan B.

Frontiers in Integrative Neuroscience; Lausanne (Oct 18, 2018). DOI:10.3389/fnint.2018.00051

ABSTRACT

Neurological therapeutics have been hampered by its inability to advance beyond symptomatic treatment of neurodegenerative disorders into the realm of actual palliation, arrest or reversal of the attendant pathological processes. While cannabis-based medicines have demonstrated safety, efficacy and consistency sufficient for regulatory approval in spasticity in multiple sclerosis, and in Dravet and Lennox-Gastaut syndromes, many therapeutic challenges remain. This review will examine the intriguing promise that recent discoveries regarding cannabis-based medicines offer to neurological therapeutics by incorporating the neutral phytocannabinoids tetrahydrocannabinol, cannabidiol, their acidic precursors, tetrahydrocannabinolic acid and cannabidiolic acid, and cannabis terpenoids in the putative treatment of five syndromes, currently labeled recalcitrant to therapeutic success, and wherein improved pharmacological intervention is required: intractable epilepsy, brain tumors, Parkinson disease, Alzheimer disease, and traumatic brain injury/chronic traumatic encephalopathy. Current basic science and clinical investigations support the safety and efficacy of such interventions in treatment of these currently intractable conditions, that in some cases share pathological processes, and the plausibility of interventions that harness endocannabinoid mechanisms, whether mediated via direct activity on CB1 and CB2 (THC, caryophyllene), PPARγ (THCA), 5-HT1A (CBD, CBDA) or even nutritional approaches utilizing prebiotics and probiotics. The inherent polypharmaceutical properties of cannabis botanicals offer distinct advantages over the current single-target pharmaceutical model and portend to revolutionize neurological treatment into a new reality of effective interventional and even preventative treatment.

DETAILS

Author: Russo, Ethan B

Publication title: Frontiers in Integrative Neuroscience; Lausanne

Publication year: 2018

Publication date: Oct 18, 2018

Country of publication: Switzerland, Lausanne

ProQuest document ID: 2288771176

Document URL: https://search.proquest.com/docview/2288771176?accountid=47765

Hemp Headway

Anonymous.

Alternative Medicine; Mendota Heights Iss. 41, (Aug 2018): 26-27.

ABSTRACT

The 2018 Farm Bill included a provision moving the US Industrial Hemp laws from a research and development pilot to a full agricultural commodity-status and effectively removed hemp-derived CBD (cannabidiol), and all naturally occurring cannabinoids therein, from the controlled-substance list. To achieve this safety standard on its product, comprehensive toxicological, pre-clinical studies investigate the safety of oral consumption of the CV Science, hemp-derived CBD oil. According to Dr. Lopez, CV Sciences' products contain a full-spectrum of other phytocannabinoids, like CBDA, THCA, CBDV, CBC and CBG to name a few.

DETAILS

Author: Anonymous

Publication title: Alternative Medicine; Mendota Heights

Issue: 41

Pages: 26-27

Publication year: 2018

Publication date: Aug 2018

Publisher: InnoVision Health Media, Inc.

Place of publication: Mendota Heights

Country of publication: United States, Mendota Heights

Publication subject: Alternative Medicine

ProQuest document ID: 2262686250

Document URL: https://search.proquest.com/docview/2262686250?accountid=47765

Effect of prior foot shock stress and [Delta]^sup 9^-tetrahydrocannabinol, cannabidiolic acid, and cannabidiol on anxiety-like responding in the light-dark emergence test in rats

Rock, Erin M; Limebeer, Cheryl L; Petrie, Gavin N; Williams, Lauren A; Mechoulam, Raphael; et al.

Psychopharmacology; Heidelberg Vol. 234, Iss. 14, (Jul 2017): 2207-2217. DOI:10.1007/s00213-017-4626-5

ABSTRACT

Rationale

Cannabis is commonly used by humans to relieve stress.

Objectives and methods

Here, we evaluate the potential of intraperitoneally (i.p.) administered [Delta]^9-tetrahydrocannabiol (THC) and cannabidiolic acid (CBDA, the precursor of cannabidiol [CBD]) to produce dose-dependent effects on anxiety-like responding in the light-dark (LD) emergence test of anxiety-like responding in rats, when administered acutely or chronically (21 days). As well, we evaluate the potential of THC, CBDA, and CBD to reduce anxiogenic responding produced by foot shock (FS) stress 24 h prior to the LD test.

Results

In the absence of the explicit FS stressor, THC (1 and 10 mg/kg) produced anxiogenic-like responding when administered acutely or chronically, but CBDA produced neither anxiogenic- nor anxiolytic-like responding. Administration of FS stress 24 h prior to the LD test enhanced anxiogenic-like responding (reduced time spent and increased latency to enter the light compartment) in rats pretreated with either vehicle (VEH) or THC (1 mg/kg); however, administration of CBDA (0.1-100 [mu]g/kg) or CBD (5 mg/kg) prevented the FS-induced anxiogenic-like responding (an anxiolytic-like effect). The 5-hydroxytryptamine 1A (5-HT$_{1A}$) receptor antagonist, WAY100635, reversed CBDA's anxiolytic effect (1 [mu]g/kg). Combining an anxiolytic dose of CBDA (1 [mu]g/kg) or CBD (5 mg/kg) with an anxiogenic dose of THC (1 mg/kg) did not modify THC's anxiogenic effect.

Conclusion

These results suggest the anxiolytic effects of CBDA and CBD may require the presence of a specific stressor.

DETAILS

Author: Rock, Erin M [1] ; Limebeer, Cheryl L [1] ; Petrie, Gavin N [1] ; Williams, Lauren A [1] ; Mechoulam, Raphael [2] ; Parker, Linda A [1]

Publication title: Psychopharmacology; Heidelberg

Volume: 234

Issue: 14

Pages: 2207-2217

Publication year: 2017

Publication date: Jul 2017

Publisher: Springer Nature B.V.

Place of publication: Heidelberg

Country of publication: Netherlands, Heidelberg

Publication subject: Pharmacy And Pharmacology

ProQuest document ID: 1912487305

Document URL: https://search.proquest.com/docview/1912487305?accountid=47765

Evaluation of cannabinoids concentration and stability in standardized preparations of cannabis tea and cannabis oil by ultra-high performance liquid chromatography tandem mass spectrometry

Pacifici, Roberta; Marchei, Emilia; Salvatore, Francesco; Guandalini, Luca; Busardò, Francesco Paolo; et al.

Clinical Chemistry and Laboratory Medicine: CCLM; Berlin Vol. 55, Iss. 10, (2017): 1555-1563. DOI:10.1515/cclm-2016-1060

ABSTRACT

Cannabis has been used since ancient times to relieve neuropathic pain, to lower intraocular pressure, to increase appetite and finally to decrease nausea and vomiting. The combination of the psychoactive cannabis alkaloid Δ9-tetrahydrocannabinol (THC) with the non-psychotropic alkaloids cannabidiol (CBD) and cannabinol (CBN) demonstrated a higher activity than THC alone. The Italian National Institute of Health sought to establish conditions and indications on how to correctly use nationally produced cannabis to guarantee therapeutic continuity in individuals treated with medical cannabis.

Methods:
The evaluation of cannabinoids concentration and stability in standardized preparations of cannabis tea and cannabis oil was conducted using an easy and fast ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) assay.

Results:

Extraction efficiency of oil was significantly higher than that of water with respect to the different cannabinoids. This was especially observed in the case of the pharmacologically active THC, CBD and their acidic precursors. Fifteen minutes boiling was sufficient to achieve the highest concentrations of cannabinoids in the cannabis tea solutions. At ambient temperature, a significant THC and CBD decrease to 50% or less of the initial concentration was observed over 3 and 7 days, respectively. When refrigerated at 4 °C, similar decreasing profiles were observed for the two compounds. The cannabinoids profile in cannabis oil obtained after pre-heating the flowering tops at 145 °C for 30 min in a static oven resulted in a complete decarboxylation of cannabinoid acids CBDA and THCA-A. Nevertheless, it was apparent that heat not only decarboxylated acidic compounds, but also significantly increased the final concentrations of cannabinoids in oil. The stability of cannabinoids in oil samples was higher than that in tea samples since the maximum decrease (72% of initial concentration) was observed in THC coming from unheated flowering tops at ambient temperature. In the case of the other cannabinoids, at ambient and refrigerated temperatures, 80%-85% of the initial concentrations were measured up to 14 days after oil preparation.

Conclusions:
As the first and most important aim of the different cannabis preparations is to guarantee therapeutic continuity in treated individuals, a strictly standardized preparation protocol is necessary to assure the availability of a homogeneous product of defined stability.

DETAILS

Author: Pacifici, Roberta; Marchei, Emilia; Salvatore, Francesco; Guandalini, Luca; Busardò, Francesco Paolo; Pichini, Simona

Publication title: Clinical Chemistry and Laboratory Medicine: CCLM; Berlin

Volume: 55

Issue: 10

Pages: 1555-1563

Publication year: 2017

Publication date: 2017

Publisher: Walter De Gruyter & Company

Place of publication: Berlin

Country of publication: Germany, Berlin

Publication subject: Biology--Biochemistry

ProQuest document ID: 1935445004

Document URL: https://search.proquest.com/docview/1935445004?accountid=47765

Effect of combined oral doses of Δ(9)-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models.

Rock, Erin M; Connolly, Cassidy; Limebeer, Cheryl L; Parker, Linda A; National Library of Medicine.

Psychopharmacology Vol. 233, Iss. 18, (September 2016): 3353-3360. DOI:10.1007/s00213-016-4378-7

ABSTRACT

RATIONALE
The purpose of this study was to evaluate the potential of oral combined cannabis constituents to reduce nausea.

OBJECTIVE
The objective of this study was to determine the effect of combining subthreshold oral doses of Δ(9)-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models of conditioned gaping.

MATERIAL AND METHODS
The potential of intragastric (i.g.) administration of THC, CBDA, or combined doses, to interfere with acute nausea-induced conditioned gaping (acute nausea) or the expression of contextually elicited conditioned gaping (anticipatory nausea), was evaluated.

RESULTS
For acute nausea, i.g. administration of subthreshold doses of THC (0.5 and 1 mg/kg) or CBDA (0.5 and 1 μg/kg) significantly suppressed acute nausea-induced gaping, whereas higher individual doses of both THC and CBDA were maximally effective. Combined i.g. administration of higher doses of THC and CBDA (2.5 mg/kg THC-2.5 μg/kg CBDA; 10 mg/kg THC-10 μg/kg CBDA; 20 mg/kg THC-20 μg/kg CBDA) also enhanced positive hedonic reactions elicited by saccharin solution during conditioning. For anticipatory nausea, combined subthreshold i.g. doses of THC (0.1 mg/kg) and CBDA (0.1 μg/kg) suppressed contextually elicited conditioned gaping. When administered i.g., THC was effective on its own at doses ranging from 1 to 10 mg/kg, but CBDA was only effective at 10 μg/kg. THC alone was equally effective by intraperitoneal (i.p.) and i.g. administration, whereas CBDA alone was more effective by i.p. administration (Rock et al. in Psychopharmacol (Berl) 232:4445-4454, 2015) than by i.g. administration.

CONCLUSIONS
Oral administration of subthreshold doses of THC and CBDA may be an effective new treatment for acute nausea and anticipatory nausea and appetite enhancement in chemotherapy patients.

DETAILS

Correspondence author: Rock, Erin M

Publication title: Psychopharmacology

Journal abbreviation: Psychopharmacology (Berl.)

Grant: 137122. Canada.

Volume: 233

Issue: 18

Pages: 3353-3360

Otsuka Pharmaceutical Co., Ltd.; Researchers Submit Patent Application, "Phytocannabinoids for Use in the Treatment of Cancer", for Approval

Women's Health Weekly; Atlanta [Atlanta]28 Aug 2014: 251

ABSTRACT

"Cannabinoids have been shown to have an anti-proliferative effect on different cancer cell lines. The cannabinoids THC, THCA, CBD, CBDA, CBG and CBC and the cannabinoid BDS THC and CBD were tested on eight different cell lines including DU-145 (hormone-sensitive prostate cancer), MDA-MB-231 (breast cancer), CaCo-2 (colorectal cancer) and C6 (glioma cells). (Ligresti, 2006).

"The anti-proliferative effects of CBD have also been evaluated on U87 and U373 human glioma cell lines, (Massi, 2004). The anti-proliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and single-strand DNA staining, which was not reverted by cannabinoid antagonists. In addition CBD, administered subcutaneously to nude mice at the dose of 0.5 mg/mouse, significantly inhibited the growth of subcutaneously implanted U87 human glioma cells. It was concluded that CBD was able to produce a significant anti-tumour activity both in vitro and in vivo, thus suggesting a possible application of CBD as a chemotherapeutic agent.

"The application WO 2006/037981 describes the use of the cannabinoid CBD to prevent tumour cells migrating or metastasising from an area of uncontrolled growth to an area away from the original tumour site. CBD caused a concentration-dependent inhibition of the migration of U87 glioma cells, quantified in a Boyden chamber. Since these cells express both cannabinoid CB1 and CB2 receptors in the membrane, the group also evaluated their engagement in the anti-migratory effect of CBD.

DETAILS

People: Alexandra, Ruth

Title: Otsuka Pharmaceutical Co., Ltd.; Researchers Submit Patent Application, "Phytocannabinoids for Use in the Treatment of Cancer", for Approval

Publication title: Women's Health Weekly; Atlanta

First page: 251

Publication year: 2014

Publication date: Aug 28, 2014

Publisher: NewsRx

Place of publication: Atlanta

Country of publication: United States, Atlanta

ProQuest document ID: 1554548179

Document URL: https://search.proquest.com/docview/1554548179?accountid=47765

Breast Cancer; Researchers' Work from Daiichi University of Pharmacy Focuses on Breast Cancer

Women's Health Weekly; Atlanta [Atlanta]22 Nov 2012: 49.

ABSTRACT

2012 NOV 22 (NewsRx) -- By a News Reporter-Staff News Editor at Women's Health Weekly -- New research on Breast Cancer is the subject of a report. According to news originating from Fukuoka, Japan, by NewsRx correspondents, research stated, "Cannabidiol (CBD), a major non-psychotropic constituent of fiber-type cannabis plant, has been reported to possess diverse biological activities, including anti-proliferative effect on cancer cells. Although CBD is obtained from non-enzymatic decarboxylation of its parent molecule, cannabidiolic acid (CBDA), few studies have investigated whether CBDA itself is biologically active."

DETAILS

Title: Breast Cancer; Researchers' Work from Daiichi University of Pharmacy Focuses on Breast Cancer

Publication title: Women's Health Weekly; Atlanta

First page: 49

Publication year: 2012

Publication date: Nov 22, 2012

Publisher: NewsRx

Place of publication: Atlanta

Country of publication: United States, Atlanta

Publication subject: Medical Sciences, Women's Interests

ProQuest document ID: 1151809854

Document URL: https://search.proquest.com/docview/1151809854?accountid=47765

Medical cannabis: prescribing and research developments

Aysha Mendes, Journal of Prescribing PracticeVol. 1, No. 6

Published Online:12 Jun 2019, https://doi.org/10.12968/jprp.2019.1.6.272

Last year, the UK Government officially recognised the medicinal value of cannabis and acknowledged that it should be available on prescription (**Torjesen, 2018**). It announced that medicinal cannabis would be available via prescription from autumn 2018, but it has been more difficult than anticipated for patients to obtain it as a result of various barriers, such as the sparse evidence available regarding its risks and benefits (**Robinson, 2019**).

There are thousands of children and adults in the UK who are living with conditions that are not treatable by currently licensed drugs and for whom medicinal cannabis may be of benefit (**Godlee, 2018**). Medicinal cannabis has been found to help chronic pain, spasticity, nausea and vomiting, and epilepsy. There is new evidence of its use in anxiety, sleep disorders, reduced appetite during chemotherapy, fibromyalgia, post-traumatic stress disorder, Parkinson's disease, agitation in dementia, bladder dysfunction, glaucoma, and Tourette's syndrome, according to a prominent British neurologist (**Godlee, 2018**).

Dr Barnes was quoted in an editorial in the *British Medical Journal* clarifying that: 'Serious side effects, including psychosis, are mainly linked to products with a high ratio of [tetrahydrocannabinol (THC)] to [cannabidiol (CBD)]' (**Godlee, 2018**), and this particular claim has most recently been evidenced in a new study by **Wall et al (2019)**.

What are researchers saying?

The recently published study in the *Journal of Psychopharmacology* has revealed that although cannabis does have some harmful effects on the areas of the brain involved in processing sensory and emotional inputs, CBD appears to serve as a buffer against these effects (**Wall et al, 2019**).

Functional magnetic resonance imaging (MRI) was used on 17 healthy volunteers who were experienced with cannabis, but not regular users (**Wall et al, 2019**). The scans took place after the participants took strains of cannabis with the main psychoactive component, Δ9-THC, and either high CBD or negligible CBD (**Clinical Pharmacist, 2019**). The volunteers who took the low CBD strain had disruptions in the brain in the regions responsible for emotional and sensory processing. The participants who took the high CBD strain, however, had minimal effects in these areas (**Clinical Pharmacist, 2019**).

These findings support the idea that THC is the cause of the harmful effects observed in cannabis users. Importantly, the authors point out that strong cannabis varieties have virtually no CBD, which appears to counteract negative effects on the parts of the brain studied, and are those linked with addiction and psychosis (**Clinical Pharmacist, 2019**). This information is important for prescribers who wish to advise their patients about various strains of medicinal cannabis and their risk and benefit profiles.

Another study published in the *Journal of Palliative Medicine* found that people living with cancer who use medical cannabis to treat their symptoms, such as neuropathic pain, have a tendency to favour strains with a higher ratio of THC to CBD, compared with patients who are taking the drug for conditions other than cancer (**Kim et al, 2019**).

Data were used from 11 590 adults who were licensed to receive medical cannabis in New York in 2016–2017, 1990 of whom were living with cancer (**Kim et al, 2019**). The researchers concluded that further studies are needed in order to understand the potential risks and benefits of cannabis for different conditions. The authors offered a possible explanation for the preference for high THC strains among people with cancer: the higher prevalence of neuropathic pain experienced by people living with cancer (**Kim et al, 2019**).

It is important to note, however, that the study did find that the THC:CBD ratio increased over time for both cancer and non-cancer patients (**Kim et al, 2019**). This would imply that a resistance does build up requiring higher doses, and this is important to know for prescribers providing relevant information to patients who are looking to make an informed decision about their treatment options.

What are politicians saying?

The evidence-base for medical cannabis is not substantial and although many patients are in need of prescriptions for various conditions, several barriers stand in the way of prescriptions becoming mainstream (**Robinson, 2019**).

In the House of Commons in April 2019, Secretary of State for Health and Social Care, Matt Hancock, was asked by Sir Mike Penning, Conservative MP for Hemel Hempstead, to ensure medical cannabis be made available on

prescription throughout England (**Robinson, 2019**). The health secretary responded that the fact the drug is still not available to parents who feel it will benefit their children is a source of immense frustration (**Robinson, 2019**).

He has therefore ordered a 'rapid evaluation' from NHS England 'to address barriers to clinically appropriate prescribing' and has also requested that the National Institute for Health Research as well as industry take action towards improving the current evidence base (**Robinson, 2019**).

Sir Mike Penning raised the point that prescriptions for medical cannabis were in fact being issued by the 'relevant experts', but that NHS Trusts and clinical commissioning groups were refusing to honour those prescriptions (**Robinson, 2019**). Matt Hancock committed, however, that if a patient needs medical cannabis and a clinician signs off on that need, the prescription will be filled (**Robinson, 2019**).

Of course there are risks and benefits to all treatments, and the Secretary of State for Health and Social Care notes that as usual, it is up to clinicians to use their judgement regarding what is known about the drug, and what is needed for an individual patient (**Robinson, 2019**).

Health Education England is also developing a training package to provide the necessary information and support to clinicians looking to make the best, most informed prescribing decisions for their patients and the Health Secretary has said that this package should be available 'imminently' (**Robinson, 2019**).

To the future

Views, practices and laws are beginning to change around the world with regards to the use of medical cannabis, and as the evidence-base catches up, it will become less taboo to include medical cannabis as part of the range of possible prescriptions for various conditions.

'Medicinal cannabis has been found to help chronic pain, spasticity, nausea and vomiting, and epilepsy'

Health Education England and the National Institute for Health and Care Excellence also urge prescribers to make use of the evidence search at https://www.evidence.nhs.uk, which provides open access to a synthesis of secondary evidence from over 800 sources, Clinical Knowledge Summaries, systematic reviews, the Scottish Intercollegiate Guidelines Network, the Cochrane Library, the royal colleges, Public Health England, and GOV.UK to everyone in the UK (**Spring et al, 2018**).

It also contains information from the *British National Formularies*, which importantly provide information on cannabis extract indications, side effects, drug interactions and contraindications – all of which will be important for non-medical prescribers to remain up-to-date with. Reviews are available via this evidence search on the use of cannabis in the treatment of epilepsy, neuropathic pain, fibromyalgia, HIV/AIDS, and asthma (**Spring et al, 2018**).

An evaluation of the anti-hyperalgesic effects of cannabidiolic acid-methyl ester in a preclinical model of peripheral neuropathic pain

Yong Fang Zhu , Katja Linher-Melville, Mohammad Javad Niazmand, Manu Sharma, Ayesha Shahid, Kan Lun Zhu, Natalka Parzei, Jesse Sidhu, Christeene Haj, Raphael Mechoulam, Gurmit Singh

First published: 24 January 2020, https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.14997

ABSTRACT

Background and Purpose

Chronic neuropathic pain (NEP) is associated with growing therapeutic cannabis use. To promote quality of life without psychotropic effects, cannabinoids other than Δ9-tetrahydrocannabidiol, including cannabidiol and its precursor cannabidiolic acid (CBDA), are being evaluated. Due to its instability, CBDA has been understudied, particularly as an anti-nociceptive agent. Adding a methyl ester group (CBDA-ME) significantly enhances its stability, facilitating analyses of its analgesic effects in vivo. This study examines early treatment efficacy of CBDA-ME in a rat model of peripherally induced NEP and evaluates sex as a biological variable.

Experimental Approach

After 14 consecutive days of intraperitoneal CBDA-ME administration at 0.01, 0.1 and 1 μg·kg^{-1}, commencing 1 day after surgically implanting a sciatic nerve-constricting cuff to induce NEP, the anti-nociceptive efficacy of this cannabinoid was assessed in male and female Sprague–Dawley rats relative to vehicle-treated counterparts. In females, 2 and 4 μg·kg^{-1} daily doses of CBDA-ME were also evaluated. Behavioural tests were performed for hind paw mechanical and thermal withdrawal thresholds once a week for 8 weeks. At endpoint, in vivo electrophysiological recordings were obtained to characterize soma threshold changes in primary sensory neurons.

Key Results

In males, CBDA-ME elicited a significant concentration-dependent chronic anti-hyperalgesic effect, also influencing both nociceptive and non-nociceptive mechanoreceptors, which were not observed in females at any of the concentrations tested.

Conclusion and Implications

Initiating treatment of a peripheral nerve injury with CBDA-ME at an early stage post-surgery provides anti-nociception in males, warranting further investigation into potential sexual dimorphisms underlying this response.

https://www.theguardian.com/society/2019/may/05/cbd-a-marijuana-miracle-or-another-health-fad-cannabidiol-anxiety-epilepsy

CBD: a marijuana miracle or just another health fad?

The cannabis-derived compound is popping up in everything from mineral water to bath bombs. We ask experts and users if it actually works

Cannabidiol is a non-psychoactive chemical found in marijuana and hemp plants. It will be present if you smoke a joint, but is often overwhelmed by one of the other 100-plus cannabinoids found in cannabis: THC (tetrahydrocannabinol). This is the ingredient that mainly has mind-altering properties, but also now has worrying links with mental illness and violence. CBD products are allowed to contain only traces of THC, which makes them legal, and devotees claim that they have many of the benefits of cannabis with none of the drawbacks…

But does it work? And does taking CBD do us any good? Philip McGuire is a professor of psychiatry and cognitive neuroscience at King's College London; he has a special interest in psychosis and started looking into cannabidiol about 15 years ago. One of the first experiments he worked on looked at how cannabidiol works in the brains of healthy people in comparison with the impact that THC has. The results were categoric. "We basically showed that the two compounds have opposite effects on brain function," says McGuire. "So when THC is making you psychotic, it stimulates certain bits of the brain. And in these areas of the brain, CBD has the opposite effect, essentially, in the same people." To boil it down: "CBD and THC seem to be pushing in opposite directions."

Mental health is just one area of investigation for those studying cannabidiol…Billy Caldwell. The 13-year-old from County Tyrone, Northern Ireland, who has epilepsy, made headlines last summer when his cannabidiol medicine was confiscated at Heathrow. After a public outcry, the home secretary, Sajid Javid, intervened and medicinal cannabis oil can now legally be prescribed in the UK.

His medicine is Epidiolex, a purified form of cannabidiol that contains less than 0.1% THC. It has been developed by a UK company, GW Pharmaceuticals, and is recommended for the treatment of two of the rarest and most severe forms of epilepsy: Lennox-Gastaut syndrome and Dravet syndrome. When it was cleared for use in the US last year, the president of the Epilepsy Foundation called it "a true medical advancement". Treatment does, however, come at an eye-watering cost; in the US, GW estimates $36,000 (£28,000) per patient annually, though the company notes that the potential future price in the UK might be different.

One suspicion about cannabidiol is that it is an impossible panacea: some, for example, claim CBD makes them more relaxed; others that it sharpens their mind to focus on complex work problems. Can it really do both? But, for McGuire, this is less a contradiction and more an indication that we don't yet know what CBD is capable of and how best to use it. "One of the interesting things about the endocannabinoid system in the body is that it's not just in the brain but also all over the body," he explains. "And cannabidiol also appears to have beneficial effects on metabolism, on the immune system and liver function, in addition to its mental health effects."

McGuire would now like to do a worldwide trial of cannabidiol in large samples to see whether it can be a medicine, not just a research tool. "Patients with psychosis have a life expectancy that's about 20 years shorter than normal, and that's because psychosis is associated with poor physical health, especially cardiovascular health," he says. "And it's possible that – this has never been tested – but another benefit of cannabidiol in these patients is that it could help with their physical health problems."

Something, though, is missing from the CBD story: proof. And this is the detail that really worries Professor McGuire. He points out that in the trials on psychosis that he's been involved in, patients might be given 1,000mg of pure cannabidiol in a tablet; the medication for the pharmaceutical treatment of epilepsy could be 2,500mg. Compare this to a drink advertised as CBD coffee or a brownie, which may contain, for example, 5mg of CBD. And there is the issue of bioavailability: how much of a drug your body actually takes into your gut. "Of that 5mg, you might absorb 1mg or less," says McGuire. "Or none."

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/739636/Consultation_on_Cannabis-derived_medicinal_products.pdf

Re: Consultation on Cannabis-derived medicinal products

11 September 2018 - letter from Advisory Council on the Misuse of Drugs to Sajid Javid MP and Matt Hancock MP

The letter includes the following recommendations:

Recommendation 1: The Home Office, DHSC and MHRA to refine the definition of a CDMP as a priority

Recommendation 2: CDMPs meeting appropriate safety and quality standards under Schedule 2 should be exempted from the general designation of Cannabis, Cannabis resin, cannabinol and cannabinol derivatives under the Misuse of Drugs (Designation) Order 2015.

Recommendation 3: The DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to lead the development of interim guidance for clinicians considering prescribing a CDMP and pharmacists who will be required to source and dispense CDMPs (including unlicensed 'special medicinal products' and products with MHRA marketing authorisation). The ACMD supports the involvement of NICE in developing substantial guidance to replace the interim guidance in due course.

Recommendation 4: The DHSC (and its equivalent in Scotland, Wales and Northern Ireland) to develop, with stakeholders, a competency framework and training pathway for the prescribing of CDMPs to support safe and effective prescribing.

Recommendation 5: The ACMD recommends that all CDMPs should have a clear content description. The description should, as a minimum requirement, state the content of CBD and THC (in mg per unit dose or volume) in a manner that would inform the prescriber when making a clinical decision. Consideration should be given to what additional information would be helpful to prescribers.

Recommendation 6: The DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to ensure that the route of administration is stated on prescriptions to help to ensure patient safety and reduce diversion. Producers of CDMPs should be required to state the appropriate route of consumption of their product. CDMPs should not be administered by smoking.

Recommendation 7: The ACMD recommends that the DHSC (and its equivalents in Scotland, Wales and Northern Ireland) establishes mechanisms to capture and publish the clinical outcomes of the prescription and use of CDMPs.

Recommendation 8: The National Institute for Health Research (NIHR) to work with DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to co-ordinate and support a programme of clinical trials to establish a credible evidence base for short and long-term safety and clinical indications.

Recommendation 9: The Home Office, DHSC (and its equivalents in Scotland, Wales and Northern Ireland) and MHRA to develop a robust communications strategy for the public, clinicians and law enforcement to ensure that coherent messages are conveyed prior to and following the proposed rescheduling. This should clarify when these products are likely to be prescribed and the route by which they can be prescribed.

Recommendation 10: The DHSC and MHRA to consider methods to encourage pharmaceutical companies to apply for MHRA marketing authorisation for CDMPs.

Recommendation 11: The Home Office and DHSC (and its equivalents in Scotland, Wales and Northern Ireland) to commit to undertaking an evidence based review of the proposed interim approach. The ACMD looks forward to the findings of this review being made available to inform our longer-term work.

Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads.

Russo, Ethan B; Marcu, Jahan; National Library of Medicine.

Advances in pharmacology (San Diego, Calif.) Vol. 80, (2017): 67-134. DOI:10.1016/bs.apha.2017.03.004

ABSTRACT

The golden age of cannabis pharmacology began in the 1960s as Raphael Mechoulam and his colleagues in Israel isolated and synthesized cannabidiol, tetrahydrocannabinol, and other phytocannabinoids. Initially, THC garnered most research interest with sporadic attention to cannabidiol, which has only rekindled in the last 15 years through a demonstration of its remarkably versatile pharmacology and synergy with THC. Gradually a cognizance of the potential of other phytocannabinoids has developed. Contemporaneous assessment of cannabis pharmacology must be even far more inclusive. Medical and recreational consumers alike have long believed in unique attributes of certain cannabis chemovars despite their similarity in cannabinoid profiles. This has focused additional research on the pharmacological contributions of mono- and sesquiterpenoids to the effects of cannabis flower preparations. Investigation reveals these aromatic compounds to contribute modulatory and therapeutic roles in the cannabis entourage far beyond expectations considering their modest concentrations in the plant. Synergistic relationships of the terpenoids to cannabinoids will be highlighted and include many complementary roles to boost therapeutic efficacy in treatment of pain, psychiatric disorders, cancer, and numerous other areas. Additional parts of the cannabis plant provide a wide and distinct variety of other compounds of pharmacological interest, including the triterpenoid friedelin from the roots, canniprene from the fan leaves, cannabisin from seed coats, and cannflavin A from seed sprouts. This chapter will explore the unique attributes of these agents and demonstrate how cannabis may yet fulfil its potential as Mechoulam's professed "pharmacological treasure trove."

DETAILS

Correspondence author: Russo, Ethan B

Publication title: Advances in pharmacology (San Diego, Calif.)

Journal abbreviation: Adv. Pharmacol.

Volume: 80

Pages: 67-134

Number of pages: 68

Publication year: 2017

Country of publication: United States

ProQuest document ID: 1931237358

Document URL: https://search.proquest.com/docview/1931237358?accountid=47765

Cannabinoids for treating inflammatory bowel diseases: where are we and where do we go?

Hasenoehrl, Carina; Storr, Martin; Schicho, Rudolf; National Library of Medicine.

Expert review of gastroenterology & hepatology Vol. 11, Iss. 4, (April 2017): 329-337.

ABSTRACT

INTRODUCTION

Fifty years after the discovery of Δ9-tetrahydrocannabinol (THC) as the psychoactive component of Cannabis, we are assessing the possibility of translating this herb into clinical treatment of inflammatory bowel diseases (IBDs). Here, a discussion on the problems associated with a potential treatment is given. From first surveys and small clinical studies in patients with IBD we have learned that Cannabis is frequently used to alleviate diarrhea, abdominal pain, and loss of appetite. Single ingredients from Cannabis, such as THC and cannabidiol, commonly described as cannabinoids, are responsible for these effects. Synthetic cannabinoid receptor agonists are also termed cannabinoids, some of which, like dronabinol and nabilone, are already available with a narcotic prescription. Areas covered: Recent data on the effects of Cannabis/cannabinoids in experimental models of IBD and in clinical trials with IBD patients have been reviewed using a PubMed database search. A short background on the endocannabinoid system is also provided. Expert commentary: Cannabinoids could be helpful for certain symptoms of IBD, but there is still a lack of clinical studies to prove efficacy, tolerability and safety of cannabinoid-based medication for IBD patients, leaving medical professionals without evidence and guidelines.

DETAILS

Correspondence author: Hasenoehrl, Carina

Publication title: Expert review of gastroenterology & hepatology

Journal abbreviation: Expert Rev Gastroenterol Hepatol

Grant: KLI 521. Austria.

Volume: 11

Issue: 4

Pages: 329-337

Number of pages: 9

Publication year: 2017

Country of publication: England

ProQuest document ID: 1876496770

Document URL: https://search.proquest.com/docview/1876496770?accountid=47765

From Phytocannabinoids to Cannabinoid Receptors and Endocannabinoids: Pleiotropic Physiological and Pathological Roles Through Complex Pharmacology.

Ligresti, Alessia; De Petrocellis, Luciano; Di Marzo, Vincenzo; National Library of Medicine.

Physiological reviews Vol. 96, Iss. 4, (October 2016): 1593-1659.

ABSTRACT

Apart from having been used and misused for at least four millennia for, among others, recreational and medicinal purposes, the cannabis plant and its most peculiar chemical components, the plant cannabinoids (phytocannabinoids), have the merit to have led humanity to discover one of the most intriguing and pleiotropic endogenous signaling systems, the endocannabinoid system (ECS). This review article aims to describe and critically discuss, in the most comprehensive possible manner, the multifaceted aspects of 1) the pharmacology and potential impact on mammalian physiology of all major phytocannabinoids, and not only of the most famous one Δ(9)-tetrahydrocannabinol, and 2) the adaptive pro-homeostatic physiological, or maladaptive pathological, roles of the ECS in mammalian cells, tissues, and organs. In doing so, we have respected the chronological order of the milestones of the millennial route from medicinal/recreational cannabis to the ECS and beyond, as it is now clear that some of the early steps in this long path, which were originally neglected, are becoming important again. The emerging picture is rather complex, but still supports the belief that more important discoveries on human physiology, and new therapies, might come in the future from new knowledge in this field.

DETAILS

Correspondence author: Ligresti, Alessia

Publication title: Physiological reviews

Volume: 96

Issue: 4

Pages: 1593-1659

Number of pages: 67

Publication year: 2016

Country of publication: United States

http://dx.doi.org/10.1152/physrev.00002.2016

ProQuest document ID: 1820597005

Document URL: https://search.proquest.com/docview/1820597005?accountid=47765

Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms.

Allan, G Michael; Finley, Caitlin R; Ton, Joey; Perry, Danielle; Ramji, Jamil; et al.

Canadian family physician Medecin de famille canadien Vol. 64, Iss. 2, (February 2018)

ABSTRACT

OBJECTIVE

To determine the effects of medical cannabinoids on pain, spasticity, and nausea and vomiting, and to identify adverse events.

DATA SOURCES

MEDLINE, the Cochrane Database, and the references of included studies were searched.

STUDY SELECTION

Systematic reviews with 2 or more randomized controlled trials (RCTs) that focused on medical cannabinoids for pain, spasticity, or nausea and vomiting were included. For adverse events, any meta-analysis for the conditions listed or of adverse events of cannabinoids was included.

SYNTHESIS

From 1085 articles, 31 relevant systematic reviews were identified including 23 for pain, 5 for spasticity, 6 for nausea and vomiting, and 12 for adverse events. Meta-analysis of 15 RCTs found more patients taking cannabinoids attained at least a 30% pain reduction: risk ratio (RR) of 1.37 (95% CI 1.14 to 1.64), number needed to treat (NNT) of 11. Sensitivity analysis found study size and duration affected findings (subgroup differences, P ≤ .03), with larger and longer RCTs finding no benefit. Meta-analysis of 4 RCTs found a positive global impression of change in spasticity (RR = 1.45, 95% CI 1.08 to 1.95, NNT = 7). Other results were not consistently statistically significant, but when positive, a 30% or more improvement in spasticity had an NNT of 10. Meta-analysis of 7 RCTs for control of nausea and vomiting after chemotherapy found an RR of 3.60 (95% CI 2.55 to 5.09) with an NNT of 3. Adverse effects caused more patients to stop treatment (number needed to harm [NNH] of 8 to 22). Individual adverse events were very common, including dizziness (NNH = 5), sedation (NNH = 5), confusion (NNH = 15), and dissociation (NNH = 20). "Feeling high" was reported in 35% to 70% of users. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) evaluation reduced evidence ratings of benefit to low or very low.

CONCLUSION

There is reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy. They might improve spasticity (primarily in multiple sclerosis). There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain and the benefit is likely small. Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy.

DETAILS

Correspondence author: Allan, G Michael

Publication title: Canadian family physician Medecin de famille canadien

Volume: 64

Issue: 2

Pages: e78-e94

Number of pages: 1

Publication year: 2018

Country of publication: Canada

ProQuest document ID: 2003038625

Document URL: https://search.proquest.com/docview/2003038625?accountid=47765

Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: A clinically-focused systematic review.

BMC Psychiatry, 20, 1-14.

ABSTRACT

Background:
Medicinal cannabis has received increased research attention over recent years due to loosening global regulatory changes. Medicinal cannabis has been reported to have potential efficacy in reducing pain, muscle spasticity, chemotherapy-induced nausea and vomiting, and intractable childhood epilepsy. Yet its potential application in the field of psychiatry is lesser known.

Methods:
The first clinically-focused systematic review on the emerging medical application of cannabis across all major psychiatric disorders was conducted. Current evidence regarding whole plant formulations and plant-derived cannabinoid isolates in mood, anxiety, sleep, psychotic disorders and attention deficit/hyperactivity disorder (ADHD) is discussed; while also detailing clinical prescription considerations (including pharmacogenomics), occupational and public health elements, and future research recommendations. The systematic review of the literature was conducted during 2019, assessing the data from all case studies and clinical trials involving medicinal cannabis or plant-derived isolates for all major psychiatric disorders (neurological conditions and pain were omitted).

Results:
The present evidence in the emerging field of cannabinoid therapeutics in psychiatry is nascent, and thereby it is currently premature to recommend cannabinoid-based interventions. Isolated positive studies have, however, revealed tentative support for cannabinoids (namely cannabidiol; CBD) for reducing social anxiety; with mixed (mainly positive) evidence for adjunctive use in schizophrenia. Case studies suggest that medicinal cannabis may be beneficial for improving sleep and post-traumatic stress disorder, however evidence is currently weak. Preliminary research findings indicate no benefit for depression from high delta-9 tetrahydrocannabinol (THC) therapeutics, or for CBD in mania. One isolated study indicates some potential efficacy for an oral cannabinoid/terpene combination in ADHD. Clinical prescriptive consideration involves caution in the use of high-THC formulations (avoidance in youth, and in people with anxiety or psychotic disorders), gradual titration, regular assessment, and caution in cardiovascular and respiratory disorders, pregnancy and breast-feeding.

Conclusions:
There is currently encouraging, albeit embryonic, evidence for medicinal cannabis in the treatment of a range of psychiatric disorders. Supportive findings are emerging for some key isolates, however, clinicians need to be mindful of a range of prescriptive and occupational safety considerations, especially if initiating higher dose THC formulas.

The pharmacokinetics and the pharmacodynamics of cannabinoids.

Lucas, Catherine J; Galettis, Peter; Schneider, Jennifer; National Library of Medicine.

British journal of clinical pharmacology Vol. 84, Iss. 11, (November 2018): 2477-2482.

ABSTRACT

There is increasing interest in the use of cannabinoids for disease and symptom management, but limited information available regarding their pharmacokinetics and pharmacodynamics to guide prescribers. Cannabis medicines contain a wide variety of chemical compounds, including the cannabinoids delta-9-tetrahydrocannabinol (THC), which is psychoactive, and the nonpsychoactive cannabidiol (CBD). Cannabis use is associated with both pathological and behavioural toxicity and, accordingly, is contraindicated in the context of significant psychiatric, cardiovascular, renal or hepatic illness. The pharmacokinetics of cannabinoids and the effects observed depend on the formulation and route of administration, which should be tailored to individual patient requirements. As both THC and CBD are hepatically metabolized, the potential exists for pharmacokinetic drug interactions via inhibition or induction of enzymes or transporters. An important example is the CBD-mediated inhibition of clobazam metabolism. Pharmacodynamic interactions may occur if cannabis is administered with other central nervous system depressant drugs, and cardiac toxicity may occur via additive hypertension and tachycardia with sympathomimetic agents. More vulnerable populations, such as older patients, may benefit from the potential symptomatic and palliative benefits of cannabinoids but are at increased risk of adverse effects. The limited availability of applicable pharmacokinetic and pharmacodynamic information highlights the need to initiate prescribing cannabis medicines using a 'start low and go slow' approach, carefully observing the patient for desired and adverse effects. Further clinical studies in the actual patient populations for whom prescribing may be considered are needed, to derive a better understanding of these drugs and enhance safe and optimal prescribing.

DETAILS

Correspondence author: Lucas, Catherine J

Publication title: British journal of clinical pharmacology

Volume: 84

Issue: 11

Pages: 2477-2482

Number of pages: 6

Publication year: 2018

Country of publication: England

ProQuest document ID: 2070239508

Document URL: https://search.proquest.com/docview/2070239508?accountid=47765

The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report.

Abrams, Donald I; National Library of Medicine.

European journal of internal medicine Vol. 49, (March 2018): 7-11.

ABSTRACT

The National Academies of Sciences, Engineering and Medicine conducted a rapid turn-around comprehensive review of recent medical literature on The Health Effects of Cannabis and Cannabinoids. The 16-member committee adopted the key features of a systematic review process, conducting an extensive search of relevant databases and considered 10,000 recent abstracts to determine their relevance. Primacy was given to recently published systematic reviews and primary research that studied one of the committee's 11 prioritized health endpoints- therapeutic effects; cancer incidence; cardiometabolic risk; respiratory disease; immune function; injury and death; prenatal, perinatal and postnatal outcomes; psychosocial outcomes; mental health; problem Cannabis use; and Cannabis use and abuse of other substances. The committee developed standard language to categorize the weight of evidence regarding whether Cannabis or cannabinoids use for therapeutic purposes are an effective or ineffective treatment for the prioritized health endpoints of interest. In the Therapeutics chapter reviewed here, the report concluded that there was conclusive or substantial evidence that Cannabis or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis. Moderate evidence was found for secondary sleep disturbances. The evidence supporting improvement in appetite, Tourette syndrome, anxiety, posttraumatic stress disorder, cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders was described as limited, insufficient or absent. A chapter of the NASEM report enumerated multiple barriers to conducting research on Cannabis in the US that may explain the paucity of positive therapeutic benefits in the published literature to date.

DETAILS

Correspondence author: Abrams, Donald I

Publication title: European journal of internal medicine

Volume: 49

Pages: 7-11

Number of pages: 5

Publication year: 2018

Country of publication: Netherlands

ProQuest document ID: 1989561362

Document URL: https://search.proquest.com/docview/1989561362?accountid=47765

Pharmacology of cannabinoids in the treatment of epilepsy

Gaston, Tyler E; Friedman, Daniel.

Epilepsy & Behavior Vol. 70, Iss. Part B, (May 2017): 313-318.

ABSTRACT

The use of *cannabis* products in the treatment of epilepsy has long been of interest to researchers and clinicians alike; however, until recently very little published data were available to support its use. This article summarizes the available scientific data of pharmacology from human and animal studies on the major cannabinoids which have been of interest in the treatment of epilepsy, including ∆9-tetrahydrocannabinol (∆9-THC), cannabidiol (CBD), ∆9-tetrahydrocannabivarin (∆9-THCV), cannabidivarin (CBDV), and ∆9-tetrahydrocannabinolic acid (Δ9-THCA). It has long been known that ∆9-THC has partial agonist activity at the endocannabinoid receptors CB1 and CB2, though it also binds to other targets which may modulate neuronal excitability and neuroinflammation. The actions of Δ9-THCV and Δ9-THCA are less well understood. In contrast to ∆9-THC, CBD has low affinity for CB1 and CB2 receptors and other targets have been investigated to explain its anticonvulsant properties including TRPV1, voltage gated potassium and sodium channels, and GPR55, among others. We describe the absorption, distribution, metabolism, and excretion of each of the above mentioned compounds. Cannabinoids as a whole are very lipophilic, resulting in decreased bioavailability, which presents challenges in optimal drug delivery. Finally, we discuss the limited drug-drug interaction data available on THC and CBD. As cannabinoids and *cannabis*-based products are studied for efficacy as anticonvulsants, more investigation is needed regarding the specific targets of action, optimal drug delivery, and potential drug-drug interactions. This article is part of a Special Issue titled Cannabinoids and Epilepsy (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: journal abstract)

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Publication title: Epilepsy & Behavior

Volume: 70

Issue: Part B

Pages: 313-318

Publication date: May 2017

Publisher: Elsevier Science (Netherlands)

Country of publication: Netherlands

ProQuest document ID: 1936334729

Document URL: https://search.proquest.com/docview/1936334729?accountid=47765