STRESSED AND DEPRESSED ASSOCIATION

ABSTRACTS OF RECENT MEDICAL RESEARCH ON CANNABIS

*The following is a small sample of abstracts from the **hundreds** of research studies happening **annually** on cannabis, cannabinoids, and the endocannabinoid regulatory system. For more information, we suggest the following resources:*

ON-LINE RESOURCES

Canadian Consortium for the Investigation of Cannabinoids (CCIC)
The CCIC is a federally registered Canadian nonprofit organization of basic and clinical researchers and health care professionals established to promote evidence-based research and education concerning the therapeutic uses of cannabinoids.
www.ccic.net

Accredited Cannabinoid Education (ACE) Program
The CCIC has designed this program for physicians and health care professionals to learn about the therapeutic uses of cannabis and cannabinoids in clinical practice. It is accredited through McGill University's Center for continuing Health Professional Education. Information on the program as well as its on-line archives can be accessed through the CCIC website above

The Endocannabinoid System Network (ECSN)
The mission of the ECSN is to serve as a multifaceted educational resource that will help scientists and clinicians understand and communicate the mechanisms and functions of the endo-cannabinoid system (ECS) — integrating knowledge of the cellular/molecular basis with the neural and systemic effects.
www.endocannabinoid.net

International Cannabinoid Research Society (ICRS)
The ICRS is dedicated to scientific research in all fields of the cannabinoids. In addition to acting as a source for impartial information on cannabis and the cannabinoids, the main role of the ICRS is to provide an open forum for researchers to meet and discuss their results.
www.cannabinoidsociety.org

BC Compassion Club Society (BCCCS)
Detailed information on our practices and standards as Canada's oldest and largest compassion Club. Also, extensive resources and links to information regarding the medical, political, legal and social aspects of medicinal cannabis.
www.thecompassionclub.org

More abstracts of research studies can be found at pubmed.net/ by entering "cannabinoids" or "cannabis" into the search criteria.

LITERATURE ON MEDICINAL CANNABIS

Handbook of Cannabis Therapeutics: From Bench to Bedside (2006). Eds., Ethan B Russo, MD, & Franjo Grotenhermen, MD. The Haworth Press, New York.
Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential (2002). Eds., Ethan B Russo, MD, & Franjo Grotenhermen, MD. The Haworth Press, New York.
Emerging Clinical Applications for Cannabis and Cannabinoids: A Review of the Recent Scientific Literature 6th ed. 2000-2013 Published by the National Organization for the Reform of Marijuana Laws (NORML) and available through their website at **www.norml.org**. The on-line version contains links to abstracts of the 200+ studies cited in the booklet.

ACNE

Cannabidiol exerts sebostatic and anti-inflammatory effects on human sebocytes. Oláh, A., Tóth, B., Borbíró, I., et al. (2014). *The Journal of Clinical Investigation, 124(9):3713–3724.* doi:10.1172/JCI64628.

The endocannabinoid system (ECS) regulates multiple physiological processes, including cutaneous cell growth and differentiation. Here, we explored the effects of the major nonpsychotropic phytocannabinoid of Cannabis sativa, (-)-cannabidiol (CBD), on human sebaceous gland function and determined that CBD behaves as a highly effective sebostatic agent. Administration of CBD to cultured human sebocytes and human skin organ culture inhibited the lipogenic actions of various compounds, including arachidonic acid and a combination of linoleic acid and testosterone, and suppressed sebocyte proliferation via the activation of transient receptor potential vanilloid-4 (TRPV4) ion channels. Activation of TRPV4 interfered with the prolipogenic ERK1/2 MAPK pathway and resulted in the downregulation of nuclear receptor interacting protein-1 (NRIP1), which influences glucose and lipid metabolism, thereby inhibiting sebocyte lipogenesis. CBD also exerted complex anti-inflammatory actions that were coupled to A2a adenosine receptor-dependent upregulation of tribbles homolog 3 (TRIB3) and inhibition of the NF-κB signaling. Collectively, our findings suggest that, due to the combined lipostatic, antiproliferative, and anti-inflammatory effects, CBD has potential as a promising therapeutic agent for the treatment of acne vulgaris.

ADDICTION

Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. Lucas, P., Reiman, A., Earlywine, M., et al., (2013). *Addiction Research & Theory, 21(5), 435-442*. doi:10.3109/16066359.2012.733465

Background: This article examines the subjective impact of medical cannabis on the use of both licit and illicit substances via self-report from 404 medical cannabis patients recruited from four dispensaries in British Columbia, Canada. The aim of this study is to examine a phenomenon called substitution effect, in which the use of one product or substance is influenced by the use or availability of another.
Methods: Researchers teamed with staff representatives from four medical cannabis dispensaries located in British Columbia, Canada to gather demographic data of patient-participants as well as information on past and present cannabis, alcohol and substance use. A 44-question survey was used to anonymously gather data on the self-reported impact of medical cannabis on the use of other substances.
Results: Over 41% state that they use cannabis as a substitute for alcohol ($n = 158$), 36.1% use cannabis as a substitute for illicit substances ($n = 137$), and 67.8% use cannabis as a substitute for prescription drugs ($n = 259$). The three main reasons cited for cannabis-related substitution are "less withdrawal" (67.7%), "fewer side-effects" (60.4%), and "better symptom management" suggesting that many patients

may have already identified cannabis as an effective and potentially safer adjunct or alternative to their prescription drug regimen.
Discussion: With 75.5% ($n = 305$) of respondents citing that they substitute cannabis for at least one other substance, and in consideration of the growing number of studies with similar findings and the credible biological mechanisms behind these results, randomized clinical trials on cannabis substitution for problematic substance use appear justified.

ADHD

Subtypes of attention deficit-hyperactivity disorder (ADHD) and cannabis use. Loflin, M., Earleywine, M., De Leo, J., et al. (2013). *Subst Use Misuse., 49(4), 427-34.* doi: 10.3109/10826084.2013.841251.

The current study examined the association between subtypes of attention-deficit/hyperactivity disorder (ADHD) and cannabis use within a sample of 2811 current users. Data were collected in 2012 from a national U.S. survey of cannabis users. A series of logistic regression equations and chi-squares were assessed for proportional differences between users. When asked about the ADHD symptoms they have experienced when not using cannabis, a higher proportion of daily users met symptom criteria for an ADHD diagnoses of the subtypes that include hyperactive-impulsive symptoms than the inattentive subtype. For nondaily users, the proportions of users meeting symptom criteria did not differ by subtype. These results have implications for identifying which individuals with ADHD might be more likely to self-medicate using cannabis. Furthermore, these findings indirectly support research linking relevant cannabinoid receptors to regulatory control.

ALS

Changes in endocannabinoid receptors and enzymes in the spinal cord of SOD1(G93A) transgenic mice and evaluation of a Sativex(®) -like combination of phytocannabinoids: interest for future therapies in amyotrophic lateral sclerosis. Moreno-Martet, M., Espejo-Porras, F., Fernández-Ruiz, J., et al. (2014). *CNS Neurosci Ther., 20(9), 809-815.* doi: 10.1111/cns.12262.

AIMS: Cannabinoids afford neuroprotection in SOD1(G93A) mutant mice, an experimental model of amyotrophic lateral sclerosis (ALS). However, these mice have been poorly studied to identify alterations in those elements of the endocannabinoid system targeted by these treatments. Moreover, we studied the neuroprotective effect of the phytocannabinoid-based medicine Sativex(®) in these mice.
METHODS: First, we analyzed the endocannabinoid receptors and enzymes in the spinal cord of SOD1(G93A) transgenic mice at a late stage of the disease. Second, 10-week-old transgenic mice were daily treated with an equimolecular combination of Δ(9) -tetrahydrocannabinol- and cannabidiol-enriched botanical extracts (20 mg/kg for each phytocannabinoid).
RESULTS: We found a significant increase of CB2 receptors and NAPE-PLD enzyme in SOD1(G93A) transgenic males and only CB2 receptors in females. Pharmacological experiments demonstrated that the treatment of these mice with the Sativex(®)-like combination of phytocannabinoids only produced weak improvements in the progression of neurological deficits and in the animal survival, particularly in females.
CONCLUSIONS: Our results demonstrated changes in endocannabinoid signaling, in particular a marked up-regulation of CB2 receptors, in SOD1(G93A) transgenic mice, and provide support that Sativex(®) may serve as a novel disease-modifying therapy in ALS.

ALZHEIMER'S

The potential therapeutic effects of THC on Alzheimer's disease. Cao, C., Li, Y., Liu, H., et al. (2014). *J Alzheimers Dis., 42(3):973-84.* doi: 10.3233/JAD-140093.

The purpose of this study was to investigate the potential therapeutic qualities of Δ9-tetrahydrocannabinol (THC) with respect to slowing or halting the hallmark characteristics of Alzheimer's disease. N2a-variant amyloid-β protein precursor (AβPP) cells were incubated with THC and assayed for amyloid-β (Aβ) levels at the 6-, 24-, and 48-hour time marks. THC was also tested for synergy with caffeine, in respect to the reduction of the Aβ level in N2a/AβPPswe cells. THC was also tested to determine if multiple treatments were beneficial. The MTT assay was performed to test the toxicity of THC. Thioflavin T assays and western blots were performed to test the direct anti-Aβ aggregation significance of THC. Lastly, THC was tested to determine its effects on glycogen synthase kinase-3β (GSK-3β) and related signaling pathways. From the results, we have discovered THC to be effective at lowering Aβ levels in N2a/AβPPswe cells at extremely low concentrations in a dose-dependent manner. However, no additive effect was found by combining caffeine and THC together. We did discover that THC directly interacts with Aβ peptide, thereby inhibiting aggregation. Furthermore, THC was effective at lowering both total GSK-3β levels and phosphorylated GSK-3β in a dose-dependent manner at low concentrations. At the treatment concentrations, no toxicity was observed and the CB1 receptor was not significantly upregulated. Additionally, low doses of THC can enhance mitochondria function and does not inhibit melatonin's enhancement of mitochondria function. These sets of data strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways.

ANXIETY/STRESS

Stress regulates endocannabinoid-CB1 receptor signaling. Hillard, C. J. (2014). *Semin Immunol., 26(5), 380-8.* doi: 10.1016/j.smim.2014.04.001.

The CB1 cannabinoid receptor is a G protein coupled receptor that is widely expressed throughout the brain. The endogenous ligands for the CB1 receptor (endocannabinoids) are N-arachidonylethanolamine and 2-arachidonoylglycerol; together the endocannabinoids and CB1R subserve activity dependent, retrograde inhibition of neurotransmitter release in the brain. Deficiency of CB1 receptor signaling is associated with anhedonia, anxiety, and persistence of negative memories. CB1 receptor-endocannabinoid signaling is activated by stress and functions to buffer or dampen the behavioral and endocrine effects of acute stress. Its role in regulation of neuronal responses is more complex. Chronic variable stress

exposure reduces endocannabinoid-CB1 receptor signaling and it is hypothesized that the resultant deficiency in endocannabinoid signaling contributes to the negative consequences of chronic stress. On the other hand, repeated exposure to the same stress can sensitize CB1 receptor signaling, resulting in dampening of the stress response. Data are reviewed that support the hypothesis that CB1 receptor signaling is stress responsive and that maintaining robust endocannabinoid/CB1 receptor signaling provides resilience against the development of stress-related pathologies.

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug. de Mello Schier, A. R., de Oliveira Ribeiro, N. P., de Oliveira e Silva, A. C., et al. (2012). *Rev. Bras. Psiquiatr., 34(1).*
doi: http://dx.doi.org/10.1590/S1516-44462012000500008.

OBJECTIVES: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa*, cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action.
METHOD: The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". The reference lists of the publications included, review articles, and book chapters were hand searched for additional references. Experimental animal and human studies were included, with no time restraints.
RESULTS: Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.
CONCLUSION: Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

APPETITE STIMULATION

The endocannabinoid system controls food intake via olfactory processes. Soria-Gomez, E., Bellocchio, L., Reguero, L., et al. (2014). *Nature Neuroscience, 17, 407–415.*
doi:10.1038/nn.3647

Hunger arouses sensory perception, eventually leading to an increase in food intake, but the underlying mechanisms remain poorly understood. We found that cannabinoid type-1 (CB_1) receptors promote food intake in fasted mice by increasing odor detection. CB_1 receptors were abundantly expressed on axon terminals of centrifugal cortical glutamatergic neurons that project to inhibitory granule cells of the main olfactory bulb (MOB). Local pharmacological and genetic manipulations revealed that endocannabinoids and exogenous cannabinoids increased odor detection and food intake in fasted mice by decreasing excitatory drive from olfactory cortex areas to the MOB. Consistently, cannabinoid agonists dampened *in vivo* optogenetically stimulated excitatory transmission in the same circuit. Our data indicate that cortical feedback projections to the MOB crucially regulate food intake via CB_1 receptor signaling, linking the feeling of hunger to stronger odor processing. Thus, CB_1 receptor–dependent control of cortical feedback projections in olfactory circuits couples internal states to perception and behavior.

ARTHRITIS

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. (2011). Lynch, M. E., & Campbell, F. (2011). *British Journal of Clinical Pharmacology, 72, 735–744.*
doi: 10.1111/j.1365-2125.2011.03970.x

Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

AUTISM

Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child. Kurz, R., & Blaas, K. (2010). *Cannabinoids, 5(4), 4-6.*

Objective: To evaluate the effectiveness of dronabinol (delta-9-THC) as supplementary therapy in a child with autistic disorder.
Methods: A child who met the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for a diagnosis of autistic disorder and who took no other medication during the observation time was included in an open and uncontrolled study. Symptom assessment was performed using the Aberrant Behavior Checklist (ABC) before and after six months of medical treatment.
Result: Compared to baseline, significant improvements were observed for hyperactivity, lethargy, irritability, stereotypy and inappropriate speech at follow-up (p=0.043).
Conclusion: This study showed that the use of dronabinol may be able to reduce the symptoms of autism.

BOWEL DISORDERS

Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Naftali, T., Bar-Lev Schleider, L., Dotan, I., et al. (2013). *Clin Gastroenterol Hepatol., 11(10), 1276-1280.* doi: 10.1016/j.cgh.2013.04.034.

BACKGROUND & AIMS: The marijuana plant *Cannabis sativa* has been reported to produce beneficial effects for patients with inflammatory bowel diseases, but this has not been investigated in controlled trials. We performed a prospective trial to determine whether cannabis can induce remission in patients with Crohn'sdisease.
METHODS: We studied 21 patients (mean age, 40 ± 14 y; 13 men) with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor-α agents. Patients were assigned randomly to groups given cannabis, twice daily, in the form of cigarettes containing 115 mg of Δ9-tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and 2 weeks thereafter.
RESULTS: Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; P = .43). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; P = .028). Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.
CONCLUSIONS: Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich cannabis produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn's disease, compared with placebo, without side effects. Further studies, with larger patient groups and a nonsmoking mode of intake, are warranted.

CANCEROUS CELLS/TUMOURS

Cannabinoids, endocannabinoids, and cancer. Hermanson, D. J., & Marnett, L. J. (2011). *Cancer and Metastasis Reviews, 30(3-4), 599-612.*

The endocannabinoid system consists of an array of endogenously produced bioactive lipids that activate cannabinoid receptors. Although the primary focus of endocannabinoid biology has been on neurological and psychiatric effects, recent work has revealed several important interactions between the endocannabinoid system and cancer. Several different types of cancer have abnormal regulation of the endocannabinoid system that contributes to cancer progression and correlates to clinical outcomes. Modulation of the endocannabinoid system by pharmacological agents in various cancer types reveals that it can mediate antiproliferative and apoptotic effects by both cannabinoid receptor-dependent and -independent pathways. Selective agonists and antagonists of the cannabinoid receptors, inhibitors of endocannabinoid hydrolysis, and cannabinoid analogs have been utilized to probe the pathways involved in the effects of the endocannabinoid system on cancer cell apoptosis, proliferation, migration, adhesion, and invasion. The antiproliferative and apoptotic effects produced by some of these pharmacological probes reveal that the endocannabinoid system is a promising new target for the development of novel chemotherapeutics to treat cancer.

CANCER TREATMENT SIDE EFFECTS

Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Machado Rocha, F. C., Stéfano, S. C., De Cássia Haiek, R., et al. (2008). *Eur J Cancer Care, 17(5), 431-43.* doi: 10.1111/j.1365-2354.2008.00917.x.

This paper aims to evaluate the anti-emetic efficacy of cannabinoids in cancer patients receiving chemotherapy using a systematic review of literature searched within electronic databases such as PUBMED, EMBASE, PSYCINFO, LILACS, and 'The Cochrane Collaboration Controlled Trials Register'. Studies chosen were randomized clinical trials comprising all publications of each database until December 2006. From 12 749 initially identified papers, 30 fulfilled the inclusion criteria for this review, with demonstration of superiority of the anti-emetic efficacy of cannabinoids compared with conventional drugs and placebo. The adverse effects were more intense and occurred more often among patients who used cannabinoids. Five meta-analyses were carried out: (1) dronabinol versus placebo [n=185; relative risk (RR)=0.47; confidence interval (CI)=0.19-1.16]; (2) Dronabinol versus neuroleptics [n=325; RR=0.67; CI=0.47-0.96; number needed to treat (NNT)=3.4]; (3) nabilone versus neuroleptics (n=277; RR=0.88; CI=0.72-1.08); (4) levonantradol versus neuroleptics (n=194; RR=0.94; CI=0.75-1.18); and (5) patients' preference for cannabis or other drugs (n=1138; RR=0.33; CI=0.24-0.44; NNT=1.8). The superiority of the anti-emetic efficacy of cannabinoids was demonstrated through meta-analysis.

CANNABIS SMOKING AND LUNG CANCER

Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Zhang, L. R., Morgenstern, H., Greenland, S., et al. (2015), *Int. J. Cancer, 136, 894–903*. doi: 10.1002/ijc.29036.

To investigate the association between cannabis smoking and lung cancer risk, data on 2,159 lung cancer cases and 2,985 controls were pooled from 6 case-control studies in the US, Canada, UK, and New Zealand within the International Lung Cancer Consortium. Study-specific associations between cannabis smoking and lung cancer were estimated using unconditional logistic regression adjusting for sociodemographic factors, tobacco smoking status and pack-years; odds-ratio estimates were pooled using random effects models. Subgroup analyses were done for sex, histology and tobacco smoking status. The shapes of dose-response associations were examined using restricted cubic spline regression. The overall pooled OR for habitual *versus* nonhabitual or never users was 0.96 (95% CI: 0.66–1.38). Compared to nonhabitual or never users, the summary OR was 0.88 (95%CI: 0.63–1.24) for individuals who smoked 1 or

more joint-equivalents of cannabis per day and 0.94 (95%CI: 0.67–1.32) for those consumed at least 10 joint-years. For adenocarcinoma cases the ORs were 1.73 (95%CI: 0.75–4.00) and 1.74 (95%CI: 0.85–3.55), respectively. However, no association was found for the squamous cell carcinoma based on small numbers. Weak associations between cannabis smoking and lung cancer were observed in never tobacco smokers. Spline modeling indicated a weak positive monotonic association between cumulative cannabis use and lung cancer, but precision was low at high exposure levels. Results from our pooled analyses provide little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effect for heavy consumption cannot be excluded.

CHRONIC PROSTATITIS

A survey of cannabis (marijuana) use and self-reported benefit in men with chronic prostatitis/chronic pelvic pain syndrome. Tripp, D. A., Nickel, J. C., Katz, L., et al. (2014). *Canadian Urological Association Journal, 8(11-12),* E901–E905. doi:10.5489/cuaj.2268.

Introduction: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic pelvic pain condition largely refractory to treatment. Cannabis (marijuana) use has been reported for a wide variety of chronic pain conditions, but no study has examined prevalence of cannabis use, symptom benefit or side effects, or frequency in CP/CPPS.
Methods: Participants were recruited from an outpatient CP/CPPS urology clinic (n = 98) and online through the Prostatitis Foundation website (n = 244). Participants completed questionnaires (demographics, CP/CPPS, depression, cannabis).
Results: The clinic sample included Canadian patients and the online sample included primarily American patients. Due to differences, groups were examined separately. Almost 50% of respondents reported using cannabis (clinic n = 49; online n = 89). Of the cannabis users, 36.8% of clinic and 75% of online respondents reported that it improved their symptoms. Most of the respondents (from the clinic and online groups) reported that cannabis improved their mood, pain, muscle spasms, and sleep. However, they did not note any improvements for weakness, fatigue, numbness, ambulation, and urination. Overall, the effectiveness of cannabis for CP/CPPS was "somewhat/very effective" (57% clinic; 63% online). There were no differences between side effects or choice of consumption and most reported using cannabis rarely.
Conclusions: These are the first estimates in men suffering from CP/CPPS and suggest that while cannabis use is prevalent, its medical use and benefit are unknown. This is an understudied area and the benefit or hazard for cannabis use awaits further study.

DEGENERATIVE DISC DISEASE

Protective effects of cannabidiol on lesion-induced intervertebral disc degeneration. Silveira, J. W., Issy, A. C., Castania, V. A., et al. (2014). *PLoS ONE, 9(12), e113161*. doi:10.1371/journal.pone.0113161.

Disc degeneration is a multifactorial process that involves hypoxia, inflammation, neoinnervation, accelerated catabolism, and reduction in water and glycosaminoglycan content. Cannabidiol is the main non-psychotropic component of the Cannabis sativa with protective and anti-inflammatory properties. However, possible therapeutic effects of cannabidiol on intervertebral disc degeneration have not been investigated yet. The present study investigated the effects of cannabidiol intradiscal injection in the coccygeal intervertebral disc degeneration induced by the needle puncture model using magnetic resonance imaging (MRI) and histological analyses. Disc injury was induced in the tail of male *Wistar* rats via a single needle puncture. The discs selected for injury were punctured percutaneously using a 21-gauge needle. MRI and histological evaluation were employed to assess the results. The effects of intradiscal injection of cannabidiol (30, 60 or 120 nmol) injected immediately after lesion were analyzed acutely (2 days) by MRI. The experimental group that received cannabidiol 120 nmol was resubmitted to MRI examination and then to histological analyses 15 days after lesion/cannabidiol injection. The needle puncture produced a significant disc injury detected both by MRI and histological analyses. Cannabidiol significantly attenuated the effects of disc injury induced by the needle puncture. Considering that cannabidiol presents an extremely safe profile and is currently being used clinically, these results suggest that this compound could be useful in the treatment of intervertebral disc degeneration.

DEPRESSION

Endocannabinoid signaling in the etiology and treatment of major depressive illness. Hillard, C. J., & Liu, Q. S. (2014). *Curr Pharm Des., 20(23), 3795-811*.

The purpose of this review is to examine human and preclinical data that are relevant to the following hypotheses. The first hypothesis is that deficient CB1R-mediated signaling results in symptoms that mimic those seen in depression. The second hypothesis is that activation of CB1R-mediated signaling results in behavioral, endocrine and other effects that are similar to those produced by currently used antidepressants. The third hypothesis is that conventional antidepressant therapies act through enhanced CB1R mediated signaling. Together the available data indicate that activators of CB1R signaling, particularly inhibitors of fatty acid amide hydrolase, should be considered for clinical trials for the treatment of depression.

The endocannabinoid system and emotional processing: a pharmacological fMRI study with Δ9-tetrahydrocannabinol. Bossong, M. G., van Hell, H. H., Jager, G., et al. (2013). *Eur Neuropsychopharmacol., 23(12), 1687-97*.
doi: 10.1016/j.euroneuro.2013.06.009.

Various psychiatric disorders such as major depression are associated with abnormalities in emotional processing. Evidence indicating involvement of the endocannabinoid system in emotional processing, and thus potentially in related abnormalities, is increasing. In the present study, we examined the role of the endocannabinoid system in processing of stimuli with a positive and negative emotional content in healthy volunteers. A pharmacological functional magnetic resonance imaging (fMRI) study was conducted with a placebo-controlled, cross-over design, investigating effects of

the endocannabinoid agonist Δ9-tetrahydrocannabinol (THC) on brain function related to emotional processing in 11 healthy subjects. Performance and brain activity during matching of stimuli with a negative ('fearful faces') or a positive content ('happy faces') were assessed after placebo and THC administration. After THC administration, performance accuracy was decreased for stimuli with a negative but not for stimuli with a positive emotional content. Our task activated a network of brain regions including amygdala, orbital frontal gyrus, hippocampus, parietal gyrus, prefrontal cortex, and regions in the occipital cortex. THC interacted with emotional content, as activity in this network was reduced for negative content, while activity for positive content was increased. These results indicate that THC administration reduces the negative bias in emotional processing. This adds human evidence to support the hypothesis that the endocannabinoid system is involved in modulation of emotional processing. Our findings also suggest a possible role for the endocannabinoid system in abnormal emotional processing, and may thus be relevant for psychiatric disorders such as major depression.

DIABETES

The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Penner, E. A., Buettner, H., & Mittleman, M. A. (2013). *The American Journal of Medicine, 126(7), 583-589.*
doi: http://dx.doi.org/10.1016/j.amjmed.2013.03.002

Background: There are limited data regarding the relationship between cannabinoids and metabolic processes. Epidemiologic studies have found lower prevalence rates of obesity and diabetes mellitus in marijuana users compared with people who have never used marijuana, suggesting a relationship between cannabinoids and peripheral metabolic processes. To date, no study has investigated the relationship between marijuana use and fasting insulin, glucose, and insulin resistance.
Methods: We included 4657 adult men and women from the National Health and Nutrition Examination Survey from 2005 to 2010. Marijuana use was assessed by self-report in a private room. Fasting insulin and glucose were measured via blood samples after a 9-hour fast, and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated to evaluate insulin resistance. Associations were estimated using multiple linear regression, accounting for survey design and adjusting for potential confounders.
Results: Of the participants in our study sample, 579 were current marijuana users and 1975 were past users. In multivariable adjusted models, current marijuana use was associated with 16% lower fasting insulin levels (95% confidence interval [CI], −26, −6) and 17% lower HOMA-IR (95% CI, −27, −6). We found significant associations between marijuana use and smaller waist circumferences. Among current users, we found no significant dose-response.
Conclusions: We found that marijuana use was associated with lower levels of fasting insulin and HOMA-IR, and smaller waist circumference.

EPILEPSY

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Porter, B. E., & Jacobson, C. (2013). *Epilepsy & Behavior, 29(3), 574-577.*
doi: http://dx.doi.org/10.1016/j.yebeh.2013.08.037

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays, and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. This survey explored the use of cannabidiol-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. Nineteen responses met the following inclusion criteria for the study: a diagnosis of epilepsy and current use of cannabidiol-enriched cannabis. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox–Gastaut syndrome and idiopathic epilepsy. The average number of antiepileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25–60% seizure reduction. Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue. Our survey shows that parents are using cannabidiol-enriched cannabis as a treatment for their children with treatment-resistant epilepsy. Because of the increasing number of states that allow access to medical cannabis, its use will likely be a growing concern for the epilepsy community. Safety and tolerability data for cannabidiol-enriched cannabis use among children are not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures.

FLU

Modulation of airway responses to Influenza A/PR/8/34 by Δ^9-Tetrahydrocannabinol in C57BL/6 mice. Buchweitz, J. P., Karmaus, P. W. F., Harkema, J. R., et al. (2007). *JPET, 323(2), 675-683.* doi:10.1124/jpet.107.124719.

Δ^9-Tetrahydrocannabinol (Δ^9-THC) has been widely established as a modulator of host immune responses. Accordingly, the objective of the present study was to examine the effects of Δ^9-THC on the immune response within the lungs and associated changes in the morphology of the bronchiolar epithelium after one challenge with a nonlethal dose of the influenza virus A/PR/8 (PR8). C57BL/6 mice were treated by oral gavage with Δ^9-THC and/or vehicle (corn oil) for 5 consecutive days. On day 3, mice were instilled intranasally with 50 plaque-forming units of PR8 and/or vehicle (saline) 4 h before Δ^9-THC exposure. Mice were subsequently killed 7 and 10 days postinfection (dpi). Viral hemagglutinin 1 (H1) mRNA levels in the lungs were

increased in a dose-dependent manner with Δ^9-THC treatment. Enumeration of inflammatory cell types in bronchoalveolar lavage fluid showed an attenuation of macrophages and $CD4^+$ and $CD8^+$ T cells in Δ^9-THC-treated mice compared with controls. Likewise, the magnitude of inflammation and virus-induced mucous cell metaplasia, as assessed by histopathology, was reduced in Δ^9-THC-treated mice by 10 dpi. Collectively, these results suggest that Δ^9-THC treatment increased viral load, as assessed by H1 mRNA levels, through a decrease in recruitment of macrophages and lymphocytes, particularly $CD4^+$ and $CD8^+$ T cells, to the lung.

HEART DISEASE

Cannabis smoking and serum C-reactive protein: A quantile regressions approach based on NHANES 2005–2010. Alshaarawy, O., & Anthony, J. C. (2015). *Drug & Alcohol Dependence, 147, 203-207.* doi: http://dx.doi.org/10.1016/j.drugalcdep.2014.11.017.

Background: Pre-clinical studies link cannabinoid-1 receptor activation to inflammation and atherosclerotic effects; anti-inflammation and immunosuppression seem to be mediated by cannabinoid-2 receptor activation. In this epidemiological study, we aim to present estimates on suspected cannabis-attributable immunomodulation as manifest in serum C-reactive protein (CRP) levels as non-specific inflammatory markers with interpretable clinical values. With strength of data from recent large nationally representative community sample surveys, the research approach illustrates value of a quantile regressions approach in lieu of the commonly used but relatively arbitrary cutpoints for CRP values.
Methods: The study population encompasses 20–59 year old participants from the National Health and Nutrition Examination Surveys, 2005–2010 (n = 1115 recently active cannabis smokers and 8041 non-smokers, identified via confidential Audio Computer Assisted Self-Interviews). Age, sex, race, education, income–poverty ratio, alcohol consumption, and tobacco smoking also were measured, together with body mass index (BMI), which actually might be on a mediational path. Quantile regressions, with bootstrapping for variance estimation, made it possible to hold these covariates constant while estimating cannabis-CRP associations.
Results: Evidence suggesting possible cannabis-attributable immunomodulation emerges at CRP levels below the median ($p < 0.05$). Whereas BMI might help explain a cannabis link with serum CRP, but BMI-stratified analyses disclosed no appreciable variation of the cannabis–CRP relationship across BMI subgroups.
Conclusions: Extending pre-clinical research on cannabis-attributable immunomodulation, this study's CRP evidence points toward possible anti-inflammatory effects of cannabis smoking. More definitive evidence can be derived by combining pre-clinical research, studies of patients, and epidemiological research approaches.

HIV/AIDS

Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T Cells. Costantino, C. M., Gupta, A., Yewdall, A. W., et al. (2012). *PLoS ONE 7(3): e33961*. doi:10.1371/journal.pone.0033961.

Agents that activate cannabinoid receptor pathways have been tested as treatments for cachexia, nausea or neuropathic pain in HIV-1/AIDS patients. The cannabinoid receptors (CB_1R and CB_2R) and the HIV-1 co-receptors, CCR5 and CXCR4, all signal via Gαi-coupled pathways. We hypothesized that drugs targeting cannabinoid receptors modulate chemokine co-receptor function and regulate HIV-1 infectivity. We found that agonism of CB_2R, but not CB_1R, reduced infection in primary CD4+ T cells following cell-free and cell-to-cell transmission of CXCR4-tropic virus. As this change in viral permissiveness was most pronounced in unstimulated T cells, we investigated the effect of CB_2R agonism on to CXCR4-induced signaling following binding of chemokine or virus to the co-receptor. We found that CB_2R agonism decreased CXCR4-activation mediated G-protein activity and MAPK phosphorylation. Furthermore, CB_2R agonism altered the cytoskeletal architecture of resting CD4+ T cells by decreasing F-actin levels. Our findings suggest that CB_2R activation in CD4+ T cells can inhibit actin reorganization and impair productive infection following cell-free or cell-associated viral acquisition of CXCR4-tropic HIV-1 in resting cells. Therefore, the clinical use of CB_2R agonists in the treatment of AIDS symptoms may also exert beneficial adjunctive antiviral effects against CXCR4-tropic viruses in late stages of HIV-1 infection.

MIGRAINE

Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Smith, S. C., & Wagner, M. S. (2014). *Neuro Endocrinol Lett., 35(3), 198-201*.

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.
METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.
RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.
CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.

MULTIPLE SCLEROSIS

Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Corey-Bloom, J.

Wolfson, T., Gamst, A., et al. (2012). *CMAJ, May 14.* doi:10.1503/cmaj.110837.

Background: Spasticity is a common and poorly controlled symptom of multiple sclerosis. Our objective was to determine the short-term effect of smoked cannabis on this symptom.
Methods: We conducted a placebo-controlled, crossover trial involving adult patients with multiple sclerosis and spasticity. We recruited participants from a regional clinic or by referral from specialists. We randomly assigned participants to either the intervention (smoked cannabis, once daily for three days) or control (identical placebo cigarettes, once daily for three days). Each participant was assessed daily before and after treatment. After a washout interval of 11 days, participants crossed over to the opposite group. Our primary outcome was change in spasticity as measured by patient score on the modified Ashworth scale. Our secondary outcomes included patients' perception of pain (as measured using a visual analogue scale), a timed walk and changes in cognitive function (as measured by patient performance on the Paced Auditory Serial Addition Test), in addition to ratings of fatigue.
Results: Thirty-seven participants were randomized at the start of the study, 30 of whom completed the trial. Treatment with smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo ($p = 0.008$). Scores for the timed walk did not differ significantly between treatment and placebo ($p = 0.2$). Scores on the Paced Auditory Serial Addition Test decreased by 8.67 points more with treatment than with placebo ($p = 0.003$). No serious adverse events occurred during the trial.
Interpretation: Smoked cannabis was superior to placebo in symptom and pain reduction in participants with treatment-resistant spasticity. Future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

NAUSEA

Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. Sharkey, K. A., Darmani, N. A., & Parker, L. A. (2014). *Eur J Pharmacol., 722, 134-146.* doi: 10.1016/j.ejphar.2013.09.068.

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

NEUROPROTECTION

Neuroprotective effects of Cannabis sativa leaves extracts on α-Motoneurons density after sciatic nerve injury in rats. Moosavie, B. Z. J., Tehranipour, M., Mollashahi, M., et al. (2013). *Life Sci J., 10(5s), 644-648.*,

Cannabis Sativa plant has many pharmacological properties. This study is aimed to investigate neuronprotective effects of extracts of this plant's leaves on α-Motor neurons in spinal cord of rats after sciatic nerve injury. Animals were divided into 6 groups (in each group N=8); A: control, B: compression, C: compression + treatment with a dose of 25 mg(kg)-1 alcoholic extract, D: compression + treatment with a dose of 50 mg(kg)-1 alcoholic extract, E: compression + treatment with a dose of 25 mg(kg)-1 aquatic extract, and F: compression + treatment with a dose of 50 mg(kg)-1 aquatic extract. After sciatic nerve compression, extract injection was done intra-peritoneal in treatment groups within 2 weeks (once a week). 28 days after compression, lumbar spinal cord was sampled and neuronal density of each group was compared with compression group. Neuronal density showed a significant difference in control and compression groups ($P<0.001$). Neuronal density had a significant increase in treatment groups compared with compression group ($P<0.001$). Aquatic and alcoholic extracts of cannabis sativa leaves have protective effects on α-Motor neurons which is probably due to antioxidant and anti-apoptotic factors in the plant extracts.

OBESITY

Cannabis and Δ9-tetrahydrocannabinol (THC) for weight loss? Le Foll, B., Trigo, J. M., Sharkey, K. A., et al. (2013). *Med Hypotheses, 80(5), 564-7.* doi: 10.1016/j.mehy.2013.01.019.

Obesity is one of the highest preventable causes of morbidity and mortality in the developed world [1]. It has been well known for a long time that exposure to cannabis produces an increase of appetite (a phenomenon referred to as the 'munchies'). This phenomenon led to an exploration of the role of the endocannabinoid system in the regulation of obesity and associated metabolic syndrome. This effort subsequently led to the development of a successful therapeutic approach for obesity that consisted of blocking the cannabinoid CB1 receptors using ligands such as Rimonabant in order to produce weight loss and improve metabolic profile [2]. Despite being efficacious, Rimonabant was associated with increased rates of depression and anxiety and therefore removed from the market. We recently discovered that the prevalence of obesity is paradoxically much lower in cannabis users as compared to non-users and that this difference is not accounted for by tobacco smoking status and is still present after adjusting for variables such as sex and age. Here, we propose that this effect is directly related to exposure to the Δ(9)-tetrahydrocannabinol (THC) present in cannabis smoke. We therefore propose the seemingly paradoxical hypothesis that THC or a THC/cannabidiol combination drug may

produce weight loss and may be a useful therapeutic for the treatment of obesity and its complications.

PAIN

Re-branding cannabis: the next generation of chronic pain medicine? Carter, G. T., Javaher, S. P., Nguyen, M. H. V., et al. (2015). *Pain Management, 5(1), 13-21*. doi:10.2217/pmt.14.49

The field of pain medicine is at a crossroads given the epidemic of addiction and overdose deaths from prescription opioids. Cannabis and its active ingredients, cannabinoids, are a much safer therapeutic option. Despite being slowed by legal restrictions and stigma, research continues to show that when used appropriately, cannabis is safe and effective for many forms of chronic pain and other conditions, and has no overdose levels. Current literature indicates many chronic pain patients could be treated with cannabis alone or with lower doses of opioids. To make progress, cannabis needs to be re-branded as a legitimate medicine and rescheduled to a more pharmacologically justifiable class of compounds. This paper discusses the data supporting re-branding and rescheduling of cannabis.

The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. Boychuk, D. G., Goddard, G., Mauro, G., et al. (2015). *Journal of Oral & Facial Pain and Headache, 29(1), 7-14.* doi: 10.11607/ofph.1274.

AIMS: To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain.
METHODS: Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta- 9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events.
RESULTS: Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.
CONCLUSION: Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Ellis, R. J., Toperoff, W., Vaida, F., et al. (2009). *Neuropsychopharmacology, 34(3), 672 680.* doi:10. l038/npp.2008. 120

Despite management with opioids and other pain modifying therapies, neuropathic pain Continues to reduce the quality of life and daily functioning in HIV-infected individuals. Cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception. We a clinical trial to assess the impact of smoked cannabis on neuropathic pain in HIV. This was a phase Il, double-blind, placebo-Controlled, crossover trial of analgesia with smoked cannabis ¡n HIV-associated distal sensory predominant polyneuropathy (DSPN). Eligible subjects had neuropathic pain refractory to at least two previous analgesic classes; they continued on their prestudy analgesic regimens throughout the trial. The primary outcome was change in pain intensity as measured by the Descriptor Differential Scale (DDS) from a pretreatment baseline to the end of each treatment week. Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size=0.60; p=0.01 6). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%Cl 0.28, 0.65) and 0.18 (0.03,0.32). Mood and daily functioning improved to a similar extent during both treatment periods. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities. Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV DSPN.

A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. Lynch, M. E., Young, J., & Clark, A. J. (2006). *Journal of Pain Symptom Management, 32(5), 497-501.*

The Canadian Marihuana Medical Access Regulations (MMAR) program allows Health Canada to grant access to marihuana for medical use to those who are suffering from grave and debilitating illnesses. This is a report on a case series of 30 patients followed at a tertiary care pain management center in Nova Scotia who have used medicinal marihuana for 1-5 years under the MMAR program. Doses of marihuana ranged from less than 1 to 5g per day via the smoked or oral route of administration. Ninety-three percent of patients reported moderate or greater pain relief. Side effects were reported by 76% of patients, the most common of which were increased appetite and a sense of well-being, weight gain, and slowed thoughts.

PARKINSON'S

Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Lotan, I., Treves, T. A., Roditi, Y., et al. (2014). *Clin Neuropharmacol., 37(2), 41-4.* doi: 10.1097/WNF.0000000000000016.

OBJECTIVE: The use of cannabis as a therapeutic agent for various medical conditions has been well documented.

However, clinical trials in patients with Parkinson disease (PD) have yielded conflicting results. The aim of the present open-label observational study was to assess the clinical effect of cannabis on motor and non-motor symptoms of PD.
METHODS: Twenty-two patients with PD attending the motor disorder clinic of a tertiary medical center in 2011 to 2012 were evaluated at baseline and 30 minutes after smoking cannabis using the following battery: Unified Parkinson Disease Rating Scale, visual analog scale, present pain intensity scale, Short-Form McGill Pain Questionnaire, as well as Medical Cannabis Survey National Drug and Alcohol Research Center Questionnaire.
RESULTS: Mean (SD) total score on the motor Unified Parkinson Disease Rating Scale score improved significantly from 33.1 (13.8) at baseline to 23.2 (10.5) after cannabis consumption ($t = 5.9$; $P < 0.001$). Analysis of specific motor symptoms revealed significant improvement after treatment in tremor ($P < 0.001$), rigidity ($P = 0.004$), and bradykinesia ($P < 0.001$).
CONCLUSIONS: There was also significant improvement of sleep and pain scores. No significant adverse effects of the drug were observed. The study suggests that cannabis might have a place in the therapeutic armamentarium of PD. Larger, controlled studies are needed to verify the results.

PSYCHOTIC DISORDERS/SCHIZOPHRENIA

Cannabidiol as a potential treatment for psychosis. Schubart, C. D., Sommer, I. E., Fusar-Poli, P., et al. (2014). *Eur Neuropsychopharmacol., 24(1), 51-64*. doi: 10.1016/j.euroneuro.2013.11.002.

Although cannabis use is associated with an increased risk of developing psychosis, the cannabis constituent cannabidiol (CBD) may have antipsychotic properties. This review concisely describes the role of the endocannabinoid system in the development of psychosis and provides an overview of currently available animal, human experimental, imaging, epidemiological and clinical studies that investigated the antipsychotic properties of CBD. In this targeted literature review we performed a search for English articles using Medline and EMBASE. Studies were selected if they described experiments with psychosis models, psychotic symptoms or psychotic disorders as outcome measure and involved the use of CBD as intervention. Evidence from several research domains suggests that CBD shows potential for antipsychotic treatment.

Alcohol and cannabis use and mortality in people with schizophrenia and related psychotic disorders. Koola, M. M., McMahon, R. P., Wehring, H. J., et al. (2012). *Journal of Psychiatric Research, 46(8), 987–993*. doi:10.1016/j.jpsychires.2012.04.019.

The impact of co-morbid substance use on mortality is not well studied in psychotic disorders. The objective of this study was to examine the impact of substance use on mortality in people with psychotic disorders and alcohol and/or drug use. We examined the rate of substance use and the risk of substance use on mortality risk over a 4–10 year period in 762 people with psychotic disorders. Deceased patients were identified from the Social Security Death Index and the Maryland Division of Vital Records. Substance use was defined as regular and heavy use or abuse or dependence. Seventy seven percent had co-morbid lifetime substance use, with co-morbid cannabis and alcohol use occurring most commonly. Out of 762 subjects, 62 died during follow up. In a Cox model, predicted mortality risk was higher in age group 35–55 compared to <35 years and in males, but reduced in cannabis users. Overall five- (3.1% vs 7.5%) and ten-year mortality risk (5.5% vs. 13.6%) was lower in cannabis users than in non-users with psychotic disorders ($p=0.005$) in a survival model. Alcohol use was not predictive of mortality. We observed a lower mortality risk in cannabis-using psychotic disorder patients compared to cannabis non-users despite subjects having similar symptoms and treatments. Future research is warranted to replicate these findings and to shed light on the anti-inflammatory properties of the endocannabinoid system and its role in decreased mortality in people with psychotic disorders.

PTSD

Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence. Passie, T., Emrich, H. M., Karst, M., et al. (2012). *Drug Test Anal., 4(7-8), 649-59*. doi: 10.1002/dta.1377.

It is known from clinical studies that some patients attempt to cope with the symptoms of post-traumatic stress disorder (PTSD) by using recreational drugs. This review presents a case report of a 19-year-old male patient with a spectrum of severe PTSD symptoms, such as intense flashbacks, panic attacks, and self-mutilation, who discovered that some of his major symptoms were dramatically reduced by smoking cannabis resin. The major part of this review is concerned with the clinical and preclinical neurobiological evidence in order to offer a potential explanation of these effects on symptom reduction in PTSD. This review shows that recent studies provided supporting evidence that PTSD patients may be able to cope with their symptoms by using cannabis products. Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories. The presence of endocannabinoid signalling systems within stress-sensitive nuclei of the hypothalamus, as well as upstream limbic structures (amygdala), point to the significance of this system for the regulation of neuroendocrine and behavioural responses to stress. Evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and antidepressive effects. It is concluded that further studies are warranted in order to evaluate the therapeutic potential of cannabinoids in PTSD.

REDUCED OPIOID OVERDOSE DEATHS

Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. Bachhuber, M. A., Saloner, B., Cunningham, C. O., et al. (2014). *JAMA Intern Med., 174(10), 1668-1673.* doi:10.1001/jamainternmed.2014.4005.

Importance: Opioid analgesic overdose mortality continues to rise in the United States, driven by increases in prescribing for chronic pain. Because chronic pain is a major indication for medical cannabis, laws that establish access to medical

cannabis may change overdose mortality related to opioid analgesics in states that have enacted them.
Objective: To determine the association between the presence of state medical cannabis laws and opioid analgesic overdose mortality.
Design, Setting, and Participants: A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.
Exposures: Presence of a law establishing a medical cannabis program in the state.
Main Outcomes and Measures: Age-adjusted opioid analgesic overdose death rate per 100 000 population in each state. Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.
Results: Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; $P = .002$), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; $P = .01$), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; $P = .04$), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; $P = .02$), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; $P = .008$), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; $P < .001$). In secondary analyses, the findings remained similar.
Conclusions and Relevance: Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.

SKIN DISEASES

Epigenetic control of skin differentiation genes by phytocannabinoids. Pucci, M., Rapino, C., Di Francesco, A., et al. (2013). *British Journal of Pharmacology, 170(3), 581-591.* doi: 10.1111/bph.12309.

Background and Purpose: Endocannabinoid signalling has been shown to have a role in the control of epidermal physiology, whereby anandamide is able to regulate the expression of skin differentiation genes through DNA methylation. Here, we investigated the possible epigenetic regulation of these genes by several phytocannabinoids, plant-derived cannabinoids that have the potential to be novel therapeutics for various human diseases.
Experimental Approach: The effects of cannabidiol, cannabigerol and cannabidivarin on the expression of skin differentiation genes keratins 1 and 10, involucrin and transglutaminase 5, as well as on DNA methylation of keratin 10 gene, were investigated in human keratinocytes (HaCaT cells). The effects of these phytocannabinoids on global DNA methylation and the activity and expression of four major DNA methyltransferases (DNMT1, 3a, 3b and 3L) were also examined.
Key Results: Cannabidiol and cannabigerol significantly reduced the expression of all the genes tested in differentiated HaCaT cells, by increasing DNA methylation of keratin 10 gene, but cannabidivarin was ineffective. Remarkably, cannabidiol reduced keratin 10 mRNA through a type-1 cannabinoid (CB_1) receptor-dependent mechanism, whereas cannabigerol did not affect either CB_1 or CB_2 receptors of HaCaT cells. In addition, cannabidiol, but not cannabigerol, increased global DNA methylation levels by selectively enhancing DNMT1 expression, without affecting DNMT 3a, 3b or 3L.
Conclusions and Implications: These findings show that the phytocannabinoids cannabidiol and cannabigerol are transcriptional repressors that can control cell proliferation and differentiation. This indicates that they (especially cannabidiol) have the potential to be lead compounds for the development of novel therapeutics for skin diseases.

SLEEP DISORDERS

Proof of concept trial of dronabinol in obstructive sleep apnea. Prasad, B., Radulovacki, M. G., & Carley, D. W. (2013). *Front. Psychiatry, 4.* doi: 10.3389/fpsyt.2013.00001.

Study Objective: Animal data suggest that Δ^9-TetraHydroCannabinol (Δ^9THC) stabilizes autonomic output during sleep, reduces spontaneous sleep-disordered breathing, and blocks serotonin-induced exacerbation of sleep apnea. On this basis, we examined the safety, tolerability, and efficacy of dronabinol (Δ^9THC), an exogenous Cannabinoid type 1 and type 2 (CB1 and CB2) receptor agonist in patients with Obstructive Sleep Apnea (OSA).
Design and Setting: Proof of concept; single-center dose-escalation study of dronabinol.
Participants: Seventeen adults with a baseline Apnea Hypopnea Index (AHI) ≥15/h. Baseline polysomnography (PSG) was performed after a 7-day washout of Continuous Positive Airway Pressure treatment.
Intervention: Dronabinol was administered after baseline PSG, starting at 2.5 mg once daily. The dose was increased weekly, as tolerated, to 5 mg and finally to 10 mg once daily.
Measurements and Results: Repeat PSG assessments were performed on nights 7, 14, and 21 of dronabinol treatment. Change in AHI (ΔAHI, mean ± SD) was significant from baseline to night 21 (-14.1 ± 17.5; $p = 0.007$). No degradation of sleep architecture or serious adverse events was noted.
Conclusion: Dronabinol treatment is safe and well-tolerated in OSA patients at doses of 2.5–10 mg daily and significantly reduces AHI in the short-term. These findings should be confirmed in a larger study in order to identify sub-populations with OSA that may benefit from cannabimimetic pharmacologic therapy.

Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex®, a cannabis-based medicine. Russo, E. B., Guy, G. W., & Robson, P. J. (2007). *Chemistry & Biodiversity, 4, 1729-1743.*

Cannabis sativa L. has been utilized for treatment of pain and sleep disorders since ancient times. This review examines modern studies on effects of D9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) on sleep. It goes on to report new information on the effects on sleep in the context of medical treatment of neuropathic pain and symptoms of multiple sclerosis, employing standardized oromucosal cannabis-based medicines containing primarily THC, CBD, or a 1 : 1 combination of the two (Sativex®). Sleep-laboratory results indicate a mild activating effect of CBD, and slight residual sedation with THC predominant extracts. Experience to date with Sativex in numerous Phase I – III studies in 2000 subjects with 1000 patient years of exposure demonstrate marked improvement in subjective sleep parameters in patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain, and rheumatoid arthritis, with an acceptable adverse event profile. No tolerance to the benefit of Sativex on pain or sleep, nor need for dosage increases have been noted in safety extension studies of up to four years, wherein 40– 50% of subjects attained good or very good sleep quality, a key source of disability in chronic pain syndromes that may contribute to patients' quality of life.

SPINAL CORD INJURY

The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. Hagenbach, U., Luz, S., Ghafoor, N., et al. (2007). *Spinal Cord. 45(8), 551-62.*

STUDY DESIGN: Open label study to determine drug dose for a randomized double-blind placebo-controlled parallel study.
OBJECTIVES: To assess the efficacy and side effects of oral Delta(9)-tetrahydrocannabinol (THC) and rectal THC-hemisuccinate (THC-HS) in SCI patients.
SETTING: REHAB Basel, Switzerland.
METHOD: Twenty-five patients with SCI were included in this three-phase study with individual dose adjustment, each consisting of 6 weeks. Twenty-two participants received oral THC open label starting with a single dose of 10 mg (Phase 1, completed by 15 patients). Eight subjects received rectal THC-HS (Phase 2, completed by seven patients). In Phase 3, six patients were treated with oral THC and seven with placebo. Major outcome parameters were the spasticity sum score (SSS) using the Modified Ashworth Scale (MAS) and self-ratings of spasticity.
RESULTS: Mean daily doses were 31 mg with THC and 43 mg with THC-HS. Mean SSS for THC decreased significantly from 16.72 (+/-7.60) at baseline to 8.92 (+/-7.14) on day 43. Similar improvement was seen with THC-HS. We observed a significant improvement of SSS with active drug (P=0.001) in the seven subjects who received oral THC in Phase 1 and placebo in Phase 3. Major reasons for drop out were increase of pain and psychological side effects.
CONCLUSION: THC is an effective and safe drug in the treatment of spasticity. At least 15-20 mg per day were needed to achieve a therapeutic effect.

STROKE

Cannabinoids in experimental stroke: a systematic review and meta-analysis. England, T. J., Hind, W. H., Rasid, N. A., et al. (2015). *J Cereb Blood Flow Metab*., *35(3), 348-358*. doi: 10.1038/jcbfm.2014.218.

Cannabinoids (CBs) show promise as neuroprotectants with some agents already licensed in humans for other conditions. We systematically reviewed CBs in preclinical stroke to guide further experimental protocols. We selected controlled studies assessing acute administration of CBs for experimental stroke, identified through systematic searches. Data were extracted on lesion volume, outcome and quality, and analyzed using random effect models. Results are expressed as standardized mean difference (SMD) with 95% confidence intervals (CIs). In all, 144 experiments (34 publications) assessed CBs on infarct volume in 1,473 animals. Cannabinoids reduced infarct volume in transient (SMD -1.41 (95% CI -1.71), -1.11) P<0.00001) and permanent (-1.67 (-2.08, -1.27), P<0.00001) ischemia and in all subclasses: endocannabinoids (-1.72 (-2.62, -0.82), P=0.0002), CB1/CB2 ligands (-1.75 (-2.19, -1.31), P<0.00001), CB2 ligands (-1.65 (-2.09, -1.22), P<0.00001), cannabidiol (-1.20 (-1.63, -0.77), P<0.00001), Δ(9)-tetrahydrocannabinol (-1.43 (-2.01, -0.86), P<0.00001), and HU-211 (-2.90 (-4.24, -1.56), P<0.0001). Early and late neuroscores significantly improved with CB use (-1.27 (-1.58, -0.95), P<0.00001; -1.63 (-2.64, -0.62), P<0.002 respectively) and there was no effect on survival. Statistical heterogeneity and publication bias was present, median study quality was 4 (range 1 to 6/8). Overall, CBs significantly reduced infarct volume and improve functional outcome in experimental stroke. Further studies in aged, female and larger animals, with other co-morbidities are required.

TRAUMATIC BRAIN INJURY

Effect of marijuana use on outcomes in traumatic brain injury. Nguyen, B. M., Kim, D., Bricker, S., et al. (2014). *The American Surgeon, 80(10), 979-983(5).*

Traumatic brain injury (TBI) is associated with significant morbidity and mortality. Several studies have demonstrated neuroprotective effects of cannabinoids. The objective of this study was to establish a relationship between the presence of a positive toxicology screen for tetrahydrocannabinol (THC) and mortality after TBI. A 3-year retrospective review of registry data at a Level I center of patients sustaining TBI having a toxicology screen was performed. Pediatric patients (younger than 15 years) and patients with a suspected nonsurvivable injury were excluded. The THC(+) group was compared with the THC(-) group with respect to injury mechanism, severity, disposition, and mortality. Logistic regression was used to determine independent associations with mortality. There were 446 cases meeting all inclusion criteria. The incidence of a positive THC screen was 18.4 per cent (82). Overall mortality was 9.9 per cent (44); however, mortality in the THC(+) group (2.4% [two]) was significantly decreased compared with the THC(-) group (11.5% [42]; P = 0.012). After adjusting for differences between the study cohorts on logistic regression, a THC(+) screen was independently associated with survival after TBI (odds ratio, 0.224; 95% confidence interval, 0.051 to 0.991; P = 0.049). A positive THC screen is associated with decreased mortality in adult patients sustaining TBI.