**Appendix e-3: Complete search strategy**

***Ovid MEDLINE***

Ovid MEDLINE(R) 1948 to February week 4 2011 # Searches Results Search Type
1 exp *cannabis/ or exp cannabis/ad, tu, ae, ct or exp cannabinoids/ad, tu, ae, ct or exp tetrahydrocannabinol/ad, tu, ae, ct or exp *cannabinoids/ or exp *tetrahydrocannabinol/ 10248 Advanced

2 exp Tic Disorders/ci, co, dt, pc, px, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Therapy] 2365 Advanced

3 exp multiple sclerosis/ci, co, dt, pc, px, th 15124 Advanced
4 Muscle Spasticity/ci, co, dt, pc, px, rh, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 2954 Advanced

5 exp migraines/ci, co, dt, pc, px, rh, th 11406 Advanced
6 Glioblastoma/ci, co, dt, pc, px, rh, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 3660 Advanced

7 exp Neurodegenerative Diseases/co, dt, pc, px, rh, th [Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 68148 Advanced

8 exp Heredodegenerative Disorders, Nervous System/co, dt, pc, px, rh, th [Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 19201 Advanced

9 exp Epilepsy/ci, co, dt, pc, px, rh, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 57400 Advanced

10 exp Nausea/ci, co, dt, pc, px, rh, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 10266 Advanced

11 exp Pain/ci, co, dt, pc, px, rh, th [Chemically Induced, Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 127471 Advanced

12 exp movement disorders/ci, co, dt, pc, px, rh, th 42688 Advanced
13 or/2-12 303938 Advanced
14 1 and 13 827 Advanced
15 limit 14 to (english language and humans) 619 Advanced
16 exp Endocannabinoids/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] 129 Advanced

17 13 and 16 23  Advanced
18 limit 17 to (english language and humans) 16  Advanced
19 15 or 18 631  Advanced
20 remove duplicates from 19 625  Advanced
21 Dystonia/co, dt, pc, px, rh, th [Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 1897  Advanced

22 exp Parkinsonian Disorders/co, dt, pc, px, rh, th [Complications, Drug Therapy, Prevention & Control, Psychology, Rehabilitation, Therapy] 24072  Advanced

23 marijuana smoking/ and (13 or 21 or 22) 91  Advanced
24 1 and (21 or 22) 32  Advanced
25 23 or 24 123  Advanced
26 ..l/ 25 lg=en and hu=y 110  Advanced
27 26 not 20 41  Advanced
28 20 or 27 666  Advanced
29 exp *cannabis/ or exp *cannabinoids/ or exp *tetracannabinols/ 9771  Advanced
30 28 and 29 549

***Ovid MEDLINE updated***

Abrams, D. I., et al. (2011). "Cannabinoid-opioid interaction in chronic pain." Clinical Pharmacology & Therapeutics **90**(6): 844-851.

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

Alenmyr, L., et al. (2011). "TRPV1 and TRPA1 stimulation induces MUC5B secretion in the human nasal airway in vivo." Clinical Physiology & Functional Imaging **31**(6): 435-444.

AIM: Nasal transient receptor potential vanilloid 1 (TRPV1) stimulation with capsaicin produces serous and mucinous secretion in the human nasal airway. The primary aim of this study was to examine topical effects of various TRP ion channel agonists on symptoms and secretion of specific mucins: mucin 5 subtype AC (MUC5AC) and B (MUC5B).

METHODS: Healthy individuals were subjected to nasal challenges with TRPV1 agonists (capsaicin, olvanil and anandamide), TRP ankyrin 1 (TRPA1) agonists (cinnamaldehyde and mustard oil) and a TRP melastatin 8 (TRPM8) agonist (menthol). Symptoms were monitored, and nasal lavages were analysed for MUC5AC and MUC5B, i.e. specific mucins associated with airway diseases. In separate groups of healthy subjects, nasal biopsies and brush samples were analysed for TRPV1 and MUC5B, using immunohistochemistry and RT-qPCR. Finally, calcium responses and ciliary beat frequency were measured on isolated ciliated epithelial cells.

RESULTS: All TRP agonists induced nasal pain or smart. Capsaicin, olvanil and mustard oil also produced rhinorrhea. Lavage fluids obtained after challenge with capsaicin and mustard oil indicated increased levels of MUC5B, whereas MUC5AC was unaffected. MUC5B and TRPV1 immunoreactivities were primarily localized to submucosal glands and peptidergic nerve fibres, respectively. Although trpv1 transcripts were detected in nasal brush samples, functional responses to capsaicin could not be induced in isolated ciliated epithelial cells.

CONCLUSION: Agonists of TRPV1 and TRPA1 induced MUC5B release in the human nasal airways in vivo. These findings may be of relevance with regard to the regulation of mucin production under physiological and pathophysiological conditions. 2011 The Authors. Clinical Physiology and Functional Imaging 2011 Scandinavian Society of Clinical Physiology and Nuclear Medicine.

Alvarez-Jaimes, L. J. and J. A. Palmer (2011). "The role of endocannabinoids in pain modulation and the therapeutic potential of inhibiting their enzymatic degradation." Current Pharmaceutical Biotechnology **12**(10): 1644-1659.

The need for new pain therapies that provide greater relief without unwanted side-effects drives the search for new drug targets. The identification of endogenous lipid ligands for the two known cannabinoid receptors (CB(1) and CB(2)) has led to numerous studies investigating the role of these endocannabinoids in pain processes. The two most widely studied endocannabinoids are anandamide (AEA; arachidonoyl ethanolamide) and 2-arachidonoylglycerol (2-AG), but there are also a number of structurally related endogenous lipid signaling molecules that are agonists at cannabinoid and noncannabinoid receptors. These lipid signaling molecules are not stored in synaptic vesicles, but are synthesized and released on-demand and act locally, as they are rapidly inactivated. This suggests that there may be therapeutic potential in modulating levels of these ligands to only have effects in active neural pathways, thereby reducing the potential for side-effects that result from widespread systemic cannabinoid receptor activation. One approach to modulate the levels and duration of action of these lipid signaling molecules is to target the enzymes responsible for their hydrolysis. The two main enzymes responsible for hydrolysis of these lipid signaling molecules are fatty acid amide hydrolase (FAAH) and monoacylglyceride lipase (MGL). This article will discuss the role of the endocannabinoid system in the modulation of pain and will review the current understanding of the properties of the hydrolytic enzymes and the recent advances in developing inhibitors for these targets, with particular relevance to the treatment of pain.

Anavi-Goffer, S., et al. (2012). "Modulation of L--lysophosphatidylinositol/GPR55 mitogen-activated protein kinase (MAPK) signaling by cannabinoids." Journal of Biological Chemistry **287**(1): 91-104.

GPR55 is activated by l--lysophosphatidylinositol (LPI) but also by certain cannabinoids. In this study, we investigated the GPR55 pharmacology of various cannabinoids, including analogues of the CB1 receptor antagonist Rimonabant, CB2 receptor agonists, and Cannabis sativa constituents. To test ERK1/2 phosphorylation, a primary downstream signaling pathway that conveys LPI-induced activation of GPR55, a high throughput system, was established using the AlphaScreen SureFire assay. Here, we show that CB1 receptor antagonists can act both as agonists alone and as inhibitors of LPI signaling under the same assay conditions. This study clarifies the controversy surrounding the GPR55-mediated actions of SR141716A; some reports indicate the compound to be an agonist and some report antagonism. In contrast, we report that the CB2 ligand GW405833 behaves as a partial agonist of GPR55 alone and enhances LPI signaling. GPR55

has been implicated in pain transmission, and thus our results suggest that this receptor may be responsible for some of the antinociceptive actions of certain CB2 receptor ligands. The phytocannabinoids 9-tetrahydrocannabivarin, cannabidivarin, and cannabigerovarin are also potent inhibitors of LPI. These Cannabis sativa constituents may represent novel therapeutics targeting GPR55.

Ashton, C. H. and P. B. Moore (2011). "Endocannabinoid system dysfunction in mood and related disorders." Acta Psychiatrica Scandinavica **124**(4): 250-261.

OBJECTIVE: The endocannabinoid (EC) system is widely distributed throughout the brain and modulates many functions. It is involved in mood and related disorders, and its activity may be modified by exogenous cannabinoids. This article examines the therapeutic potential of cannabinoids in psychiatric disorders.

METHOD: An overview is presented of the literature focussed on the functions of the EC system, its dysfunction in mood disorders and the therapeutic potential of exogenous cannabinoids.

RESULTS: We propose (hypothesize) that the EC system, which is homoeostatic in cortical excitation and inhibition, is dysfunctional in mood and related disorders. Anandamide, tetrahydrocannabinol (THC) and cannabidiol (CBD) variously combine antidepressant, antipsychotic, anxiolytic, analgesic, anticonvulsant actions, suggesting a therapeutic potential in mood and related disorders. Currently, cannabinoids find a role in pain control. Post mortem and other studies report EC system abnormalities in depression, schizophrenia and suicide. Abnormalities in the cannabinoid-1 receptor (CNR1) gene that codes for cannabinoid-1 (CB1) receptors are reported in psychiatric disorders. However, efficacy trials of cannabinoids in psychiatric disorders are limited but offer some encouragement.

CONCLUSION: Research is needed to elucidate the role of the EC system in psychiatric disorders and for clinical trials with THC, CBD and synthetic cannabinoids to assess their therapeutic potential. 2011 John Wiley & Sons A/S.

Ashton, J. C. (2012). "Synthetic cannabinoids as drugs of abuse." Current Drug Abuse Reviews **5**(2): 158-168.

In the last decade a number of products have appeared in various countries that contain synthetic cannabinoids. This article reviews the history of the sale of these drugs, and the evidence that they contain synthetic cannabinoids. The biochemistry of the synthetic cannabinoids identified thus far is discussed, including a discussion of chemical structures and biochemical targets. The cannabinoid receptor targets for these drugs are discussed, as well as other possible targets such as serotonin receptors. Evidence for the abuse potential of these drugs is reviewed. The toxicity of synthetic cannabinoids and cannabinoid products is reviewed and compared to that of the phytocannabinoid 9-tetrahydrocannabinol (THC). As cannabinoids are a structurally diverse class of drugs, it is concluded that synthetic cannabinoids should be classified by biological activity rather than by structure, and that if this isn't done, novel synthetic cannabinoids will continue to emerge that fall outside of current regulatory classification models.

Atwood, B. K., et al. (2012). "CB2: therapeutic target-in-waiting." Progress in Neuro-Psychopharmacology & Biological Psychiatry **38**(1): 16-20.

CB2 cannabinoid receptor agonists hold promise as a new class of therapeutics for indications as diverse as pain, neuroinflammation, immune suppression and osteoporosis. These potential indications are supported by strong preliminary data from multiple investigators using diverse preclinical models. However, clinical trials for CB2 agonists, when they have been reported have generally been disappointing. This review considers possible explanations for the mismatch between promising preclinical data and disappointing clinical data. We propose that a more careful consideration of CB2 receptor pharmacology may help move CB2 agonists from "promising" to "effective" therapeutics. Copyright 2012 Elsevier Inc. All rights reserved.

Bagdure, S., et al. (2012). "Waning effect of compulsive bathing in cannabinoid hyperemesis." American Journal on Addictions **21**(2): 184-185.

Bestard, J. A. and C. C. Toth (2011). "An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy." Pain Practice **11**(4): 353-368.

Neuropathic pain (NeP) is prevalent in patients with peripheral neuropathy (PN), regardless of etiology. We sought to compare the efficacy of the cannabinoid nabilone as either monotherapy or adjuvant therapy with a first-line medication for NeP, gabapentin, in a patient population with PN-NeP. Patients diagnosed with PN-NeP were permitted to initiate monotherapy (nabilone or gabapentin) or add one of these two medications (adjuvant therapy) to their existing NeP treatment regimen in a non-randomized open-label nature. Baseline data collected included a primary outcome (visual analog scores [VAS] of pain) and secondary outcomes (quality of life [EuroQol 5 Domains and Short-Form 36] assessments and assessments of sleep [Medical Outcomes Sleep Study Scale {MOSSS}], anxiety and depression [Hospital Anxiety and Depression Scale], and pain [Brief Pain Inventory]). Reassessment and modulation of dosing and/or medications occurred at 3- and 6-month intervals. Medication adverse effects and drug efficacy, as well as questionnaires, were assessed at 6 months. Matched analysis of variance testing was performed to compare 3- and 6-month scores with baseline, as well as to compare therapies at equal time points. Significant improvements in pain VAS were seen in all treatment groups at 6 months. Numerous sleep parameters within MOSSS, Brief Pain Inventory, and Short-Form 36 improved in patients receiving nabilone or gabapentin either as monotherapy or adjuvant treatment. Hospital Anxiety and Depression Scale-A scores were significantly improved in all treatment groups. Sleep adequacy and the sleep problems index within the MOSSS improved in nabilone monotherapy patients in particular. The benefits of monotherapy or adjuvant therapy with nabilone appear comparable to gabapentin for management of NeP. We advocate for head-to-head randomized, double-blind studies for current therapies for NeP in order to determine potential advantages beneficial in this patient population.

2010 The Authors. Pain Practice 2010 World Institute of Pain.

Bisogno, T. and V. Di Marzo (2010). "Cannabinoid receptors and endocannabinoids: role in neuroinflammatory and neurodegenerative disorders." CNS & Neurological Disorders Drug Targets **9**(5): 564-573.

The G-protein coupled receptors for 9-tetrahydrocannabinol, the major psychoactive principle of marijuana, are known as cannabinoid receptors of type 1 (CB1) and 2 (CB2) and play important functions in degenerative and inflammatory disorders of the central nervous system. Whilst CB1 receptors are mostly expressed in neurons, where they regulate neurotransmitter release and synaptic strength, CB2 receptors are found mostly in glial cells and microglia, which become activated and over-express these receptors during disorders such as Alzheimer's disease, multiple sclerosis, amyotropic lateral sclerosis, Parkinson's disease, and Huntington's chorea. The neuromodulatory actions at CB1 receptors by endogenous agonists ('endocannabinoids'), of which anandamide and 2-arachidonoylglycerol are the two most studied representatives, allows them to counteract the neurochemical unbalances arising during these disorders. In contrast, the immunomodulatory effects of these lipophilic mediators at CB2 receptors regulate the activity and function of glia and microglia. Indeed, the level of expression of CB1 and CB2 receptors or of enzymes controlling endocannabinoid levels, and hence the concentrations of endocannabinoids, undergo time- and brain region-specific changes during neurodegenerative and neuroinflammatory disorders, with the initial attempt to counteract excitotoxicity and inflammation. Here we discuss this plasticity of the endocannabinoid system during the aforementioned central nervous system disorders, as well as its dysregulation, both of which have opened the way to the use of either direct and indirect activators or blockers of CB1 and CB2 receptors for the treatment of the symptoms or progression of these diseases.

Booz, G. W. (2011). "Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress." Free Radical Biology & Medicine **51**(5): 1054-1061.

Oxidative stress with reactive oxygen species generation is a key weapon in the arsenal of the immune system for fighting invading pathogens and initiating tissue repair. If excessive or unresolved, however, immune-related oxidative stress can initiate further increasing levels of oxidative stress that cause organ damage and dysfunction. Targeting oxidative stress in various diseases therapeutically has proven more problematic than first anticipated given the complexities and perversity of both the underlying disease and the immune response. However, growing evidence suggests that the endocannabinoid system, which includes the CB1 and CB2 G-protein-coupled receptors and their endogenous lipid ligands, may be an area that is ripe for therapeutic exploitation. In this context, the related nonpsychotropic cannabinoid cannabidiol, which may interact with the endocannabinoid system but has actions that are distinct, offers promise as a prototype for anti-inflammatory drug development. This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of

human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain. Copyright 2011 Elsevier Inc. All rights reserved.

Bowles, D. W., et al. (2012). "The intersection between cannabis and cancer in the United States." Critical Reviews in Oncology-Hematology **83**(1): 1-10.

In the last 15 years there has been a major shift in the laws governing medical use of cannabis in the United States. Corresponding with this change there has been escalating interest in the role that cannabis, commonly referred to as marijuana, and cannabinoids play in the care of patients with cancer. This review will examine cannabis' and cannabinoids' current and potential roles in cancer care. Specifically, we will examine five areas of cannabis medicine: (1) pharmacologic properties of cannabis; (2) its potential role in the development of human cancers, particularly smoking-related malignancies; (3) cannabinoids' potential as anti-cancer therapies; (4) cannabis and cannabinoids in the palliation of common cancer-associated symptoms; (5) current legal status of cannabis for medical purposes in the United States. Copyright 2011 Elsevier Ireland Ltd. All rights reserved.

Brenna, O., et al. (2011). "A man in his 30s with recurrent vomiting and abdominal pain relieved by hot showers." Tidsskrift for Den Norske Laegeforening **131**(21): 2134-2136.

Brower, V. (2012). "New pain drugs in pipeline, but challenges to usage remain." Journal of the National Cancer Institute **104**(7): 503-505.

Brunnauer, A., et al. (2011). "Cannabinoids improve driving ability in a Tourette's patient." Psychiatry Research **190**(2-3): 382.

Capasso, R., et al. (2011). "Inhibitory effect of standardized cannabis sativa extract and its ingredient cannabidiol on rat and human bladder contractility." Urology **77**(4): 1006.e1009-1006.e1015.

OBJECTIVES: To evaluate the effect of a Cannabis sativa extract enriched in cannabidiol (CBD) botanic drug substance (BDS) and pure CBD, on bladder contractility in vitro. Cannabis based-medicines, including CBD-enriched extracts, have been shown to reduce urinary urgency, incontinence episodes, frequency, and nocturia in patients with multiple sclerosis.

METHODS: Strips were cut from male Wistar rats and the human bladder body and placed in organ baths containing Krebs solution. Contractions were induced by electrical field stimulation, acetylcholine, KCl, and ,-methylene adenosine triphosphate.

RESULTS: CBD BDS significantly reduced the contractions induced by acetylcholine, but not those induced with electrical field stimulation, KCl, or ,-methylene adenosine triphosphate in the isolated rat bladder. The inhibitory effect of CBD

BDS was not significantly modified by the cannabinoid or opioid receptor antagonists or by modulators of calcium levels, but it was increased by ruthenium red and capsazepine, 2 transient receptor potential vanilloid type-1 blockers. In humans, CBD BDS and pure CBD significantly reduced acetylcholine-induced contractions, an effect that was not changed by the transient receptor potential vanilloid type-1 blockers.

CONCLUSIONS: Our data have suggested that CBD BDS reduces cholinergic-mediated contractility and that this effect is modulated by transient receptor potential vanilloid type-1 in rats but not in humans. CBD is the chemical ingredient of CBD BDS responsible for such activity. If confirmed in vivo, such results could provide a pharmacologic basis to explain, at least in part, the efficacy of Cannabis medicines in reducing incontinence episodes in patients with multiple sclerosis. 

Carter, G. T., et al. (2011). "Cannabis in palliative medicine: improving care and reducing opioid-related morbidity." American Journal of Hospice & Palliative Medicine **28**(5): 297-303.

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.

Chen, B. C. and R. S. Hoffman (2012). "The role of cannabinoids in chronic pain patients remains hazy." Clinical Pharmacology & Therapeutics **91**(6): 972; author reply 972-973.

Cheng, Y.-X., et al. (2012). "-Carbolines: a novel class of cannabinoid agonists with high aqueous solubility and restricted CNS penetration." Bioorganic & Medicinal Chemistry Letters **22**(4): 1619-1624.

An oral, peripherally restricted CB1/CB2 agonist could provide an interesting approach to treat chronic pain by harnessing the analgesic properties of cannabinoids but without the well-known central side effects. -Carbolines are a novel class of potent mixed CB1/CB2 agonists characterized by attractive physicochemical properties including high aqueous solubility. Optimization of the series has led to the discovery of 29, which has oral activity in a rat inflammatory pain model and limited brain exposure at analgesic doses, consistent with a lower risk of CNS-mediated tolerability issues. 

Chiodi, V., et al. (2012). "Unbalance of CB1 receptors expressed in GABAergic and

glutamatergic neurons in a transgenic mouse model of Huntington's disease." Neurobiology of Disease **45**(3): 983-991.

Cannabinoid CB1 receptors (CB1Rs) are known to be downregulated in patients and in animal models of Huntington's disease (HD). However, the functional meaning of this reduction, if any, is still unclear. Here, the effects of the cannabinoid receptor agonist WIN 55,212-2 (WIN) were investigated on striatal synaptic transmission and on glutamate and GABA release in symptomatic R6/2 mice, a genetic model of HD. The expression levels of CB1Rs in glutamatergic and GABAergic synapses were also evaluated. We found that in R6/2 mice, WIN effects on synaptic transmission and glutamate release were significantly increased with respect to wild type mice. On the contrary, a decrease in WIN-induced reduction of GABA release was found in R6/2 versus WT mice. The expression of CB1Rs in GABAergic neurons was drastically reduced, while CB1Rs levels in glutamatergic neurons were unchanged. These results demonstrate that the expression and functionality of CB1Rs are differentially affected in GABAergic and glutamatergic neurons in R6/2 mice. As a result, the balance between CB1Rs expressed by the two neuronal populations and, thus, the net effect of CB1R stimulation, is profoundly altered in HD mice. Copyright 2011 Elsevier Inc. All rights reserved.

Christie, M. J. and C. W. Vaughan (2011). "Receptors: cannabis medicine without a high." Nature Chemical Biology **7**(5): 249-250.

Cobellis, L., et al. (2011). "Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study." European Journal of Obstetrics, Gynecology, & Reproductive Biology **158**(1): 82-86.

OBJECTIVE: Aim of our study was to evaluate the effectiveness of the association between N-Palmitoylethanolamine and transpolydatin in the management of chronic pelvic pain related to EMS.

STUDY DESIGN: This was a randomized, double-blind, parallel-group, placebo-controlled clinical trial involving 61 subjects, submitted to a first line laparoscopic conservative surgery, who were randomized into 3 groups receiving: group A (n=21) the association N-Palmitoylethanolamine-transpolydatin 400 mg + 40 mg twice a day for 3 months; group B (n=20) the placebo for 3 months; group C (n=20) a single course of Celecoxib 200mg twice a day for 7 consecutive days. Assessments of the severity of pelvic endometriosis (pelvic pain, dysmenorrhoea and dyspareunia) were recorded before and after treatment on a questionnaire and a 10-point VAS. Differences between groups were verified with Kruskal-Wallis ANOVA for non-parametric multiple comparisons.

RESULTS: A marked decrease in dysmenorrhoea, dyspareunia and pelvic pain was observed in all groups, and the association between N-Palmitoylethanolamine and transpolydatin resulted to be more effective than placebo (P<.001). Additionally, the treatment with Celecoxib resulted in a decrease in pelvic pain more effective either than the association N-Palmitoylethanolamine and transpolydatin or placebo.

CONCLUSION: These preliminary results show that the association between micronized N-Palmitoylethanolamine and transpolydatin is effective in the management of pelvic pain related to endometriosis after laparoscopy. Additionally, this association seems to be safe, shows an optimal control of pain and can be used in patients who are unable to receive other therapies. 

Corey-Bloom, J., et al. (2012). "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial." CMAJ Canadian Medical Association Journal **184**(10): 1143-1150.

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.

Cumella, J., et al. (2012). "Chromenopyrazoles: non-psychoactive and selective CB1 cannabinoid agonists with peripheral antinociceptive properties." ChemMedChem **7**(3): 452-463.

The unwanted psychoactive effects of cannabinoid receptor agonists have limited their development as medicines. These CB1-mediated side effects are due to the fact that CB1 receptors are largely expressed in the central nervous system (CNS). As it is known that CB1 receptors are also located peripherally, there is growing

interest in targeting cannabinoid receptors located outside the brain. A library of chromenopyrazoles designed analogously to the classical cannabinoid cannabinol were synthesized, characterized, and tested for cannabinoid activity. Radioligand binding assays were used to determine their affinities at CB1 and CB2 receptors. Structural features required for CB1/CB2 affinity and selectivity were explored by molecular modeling. Some compounds in the chromenopyrazole series were observed to be selective CB1 ligands. These modeling studies suggest that full CB1 selectivity over CB2 can be explained by the presence of a pyrazole ring in the structure. The functional activities of selected chromenopyrazoles were evaluated in isolated tissues. Invivo behavioral tests were then carried out on the most effective CB1 cannabinoid agonist, 13a. Chromenopyrazole 13a did not induce modifications in any of the tested parameters on the mouse cannabinoid tetrad, thus discounting CNS-mediated effects. This lack of agonistic activity in the CNS suggests that this compound does not readily cross the blood-brain barrier. Moreover, 13a can induce antinociception in a rat peripheral model of orofacial pain. Taking into account the negative results obtained with the hot-plate test, the antinociception induced by 13a in the orofacial test could be mediated through peripheral mechanisms. Copyright 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Cumella, J., et al. (2012). "Chromenopyrazoles: non-psychoactive and selective CB1 cannabinoid agonists with peripheral antinociceptive properties." ChemMedChem **7**(3): 452-463.

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Daganzo, S. and G. Nune (2010). "Pot shots-Cannabis arteritis of the digits." Journal of Hospital Medicine **5**(7): 424-425.

Davison, S. N. and J. S. Davison (2011). "Is there a legitimate role for the therapeutic use of cannabinoids for symptom management in chronic kidney disease?" Journal of Pain & Symptom Management **41**(4): 768-778.

Chronic pain is a common and debilitating symptom experienced in the context of numerous other physical and emotional symptoms by many patients with chronic kidney disease (CKD). Management of pain with opioids in CKD can be problematic given the prominence of adverse effects of opioids in CKD, which may exacerbate symptoms, such as nausea, anorexia, pruritus, and insomnia, all of which impact negatively on patients' health-related quality of life. Novel therapeutic approaches for pain and symptom management in CKD are required. Recent research in the area of cannabinoids (CBs) is legitimizing the use of cannabis-based medicine. In this review, we describe the symptom burden borne by patients with CKD and review some of the key basic science and clinical literature to evaluate the potential use of CBs for the management of overall symptom burden in CKD. Copyright 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

De Petrocellis, L., et al. (2011). "N-palmitoyl-vanillamide (palvanil) is a non-pungent analogue of capsaicin with stronger desensitizing capability against the TRPV1 receptor and anti-hyperalgesic activity." Pharmacological Research **63**(4): 294-299.

N-acyl-vanillamide (NAVAM) analogues of the natural pungent principle of capsicum, capsaicin, were developed several years ago as potential non-pungent analgesic compounds. N-oleoyl-vanillamide (olvanil) and N-arachidonoy-vanillamide (arvanil), in particular, were described in several publications and patents to behave as potent anti-hyperalgesic compounds in experimental models of chronic and inflammatory pain, and to activate both "capsaicin receptors", i.e. the transient receptor potential of vanilloid type-1 (TRPV1) channel, and, either directly or indirectly, cannabinoid receptors of type-1. Here we report the biochemical and pharmacological characterization of a so far neglected NAVAM, N-palmitoyl-vanillamide (palvanil), and propose its possible use instead of capsaicin, as a possible topical analgesic. Palvanil exhibited a kinetics of activation of human recombinant TRPV1-mediated intracellular calcium elevation significantly slower than that of capsaicin (t(1/2)=21s and 8s, respectively at 1uM). Slow kinetics of TRPV1 agonists were previously found to be associated with stronger potencies as TRPV1 desensitizing agents, which in turn are usually associated with lower pungency and stronger anti-hyperalgesic activity. Accordingly, palvanil desensitized the human recombinant TRPV1 to the effect of capsaicin (10nM) with significantly higher potency than capsaicin (IC(50)=0.8nM and 3.8nM, respectively), this effect reaching its maximum more rapidly (50 and 250min, respectively). Palvanil was also more potent than capsaicin at desensitizing the stimulatory effect of TRPV1 by low pH together with anandamide, which mimics conditions occurring during inflammation. In the eye-

wiping assay carried out in mice, palvanil was not pungent and instead caused a strong and long-lasting inhibition of capsaicin-induced eye-wiping. Finally, intraplantar palvanil inhibited the second phase of the nociceptive response to formalin in mice. In conclusion, palvanil appears to be a non-pungent analogue of capsaicin with stronger desensitizing effects on TRPV1 and hence potentially higher anti-hyperalgesic activity. Copyright 2011 Elsevier Ltd. All rights reserved.

de Vries, K. and A. J. Green (2012). "Therapeutic use of cannabis." Nursing Times **108**(9): 12-15.

Therapeutic cannabis use raises a number of dilemmas for nurses. This article examines the legal, political and ethical challenges raised by the use of cannabis by people with life-limiting or terminal illnesses in their own homes. (Throughout this paper, the term cannabis refers to illegal cannabis unless specified.) A literature review of databases from 1996 was conducted and internet material was also examined. Evidence on the therapeutic use of cannabis suggests it may produce improvements in quality of life, which has led to increased use among people with life-limiting illnesses. The cannabis used is usually obtained illegally, which can have consequences for both those who use it and nurses who provide treatment in the community.

Donnino, M. W., et al. (2011). "Cannabinoid hyperemesis: a case series." Journal of Emergency Medicine **40**(4): e63-66.

BACKGROUND: Cannabinoid use is prevalent in the United States, with recent reports of increased usage among younger Americans. Traditionally, cannabinoids have been used recreationally or as antiemetics; however, recent reports suggest that chronic abuse can result in the paradoxical effect of a cyclic vomiting syndrome, termed cannabinoid hyperemesis.

OBJECTIVE: We report on this recently described clinical syndrome characterized by severe nausea and hyperemesis in the setting of chronic cannabinoid use.

CASE REPORTS: We report the cases of 3 patients who presented to two academic emergency departments (EDs) on multiple occasions with nausea and vomiting in the setting of chronic cannabinoid use. There were extensive medical evaluations and frequent inpatient hospital admissions before the diagnosis of cannabinoid hyperemesis was considered.

CONCLUSION: With the relatively high prevalence of cannabinoid use in the United States and increasing interest in the applications of marijuana for therapeutic purposes, this entity may be encountered in the ED. Cannabinoid hyperemesis should be considered in the differential diagnosis of patients presenting with similar symptoms. Copyright 2011 Elsevier Inc. All rights reserved.

Downer, E. J., et al. (2011). "Identification of the synthetic cannabinoid R(+)WIN55,212-2 as a novel regulator of IFN regulatory factor 3 activation and IFN-beta expression: relevance to therapeutic effects in models of multiple sclerosis." Journal of Biological Chemistry **286**(12): 10316-10328.

-Interferons (IFN-s) represent one of the first line treatments for relapsing-

remitting multiple sclerosis, slowing disease progression while reducing the frequency of relapses. Despite this, more effective, well tolerated therapeutic strategies are needed. Cannabinoids palliate experimental autoimmune encephalomyelitis (EAE) symptoms and have therapeutic potential in MS patients although the precise molecular mechanism for these effects is not understood. Toll-like receptor (TLR) signaling controls innate immune responses and TLRs are implicated in MS. Here we demonstrate that the synthetic cannabinoid R(+)WIN55,212-2 is a novel regulator of TLR3 and TLR4 signaling by inhibiting the pro-inflammatory signaling axis triggered by TLR3 and TLR4, whereas selectively augmenting TLR3-induced activation of IFN regulatory factor 3 (IRF3) and expression of IFN-. We present evidence that R(+)WIN55,212-2 strongly promotes the nuclear localization of IRF3. The potentiation of IFN- expression by R(+)WIN55,212-2 is critical for manifesting its protective effects in the murine MS model EAE as evidenced by its reduced therapeutic efficacy in the presence of an anti-IFN- antibody. R(+)WIN55,212-2 also induces IFN- expression in MS patient peripheral blood mononuclear cells, whereas down-regulating inflammatory signaling in these cells. These findings identify R(+)WIN55,212-2 as a novel regulator of TLR3 signaling to IRF3 activation and IFN- expression and highlights a new mechanism that may be open to exploitation in the development of new therapeutics for the treatment of MS.

Duran, M., et al. (2010). "Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting." British Journal of Clinical Pharmacology **70**(5): 656-663.

AIMS: Despite progress in anti-emetic treatment, many patients still suffer from chemotherapy-induced nausea and vomiting (CINV). This is a pilot, randomized, double-blind, placebo-controlled phase II clinical trial designed to evaluate the tolerability, preliminary efficacy, and pharmacokinetics of an acute dose titration of a whole-plant cannabis-based medicine (CBM) containing delta-9-tetrahydrocannabinol and cannabidiol, taken in conjunction with standard therapies in the control of CINV.

METHODS: Patients suffering from CINV despite prophylaxis with standard anti-emetic treatment were randomized to CBM or placebo, during the 120h post-chemotherapy period, added to standard anti-emetic treatment. Tolerability was measured as the number of withdrawals from the study during the titration period because of adverse events (AEs). The endpoint for the preliminary efficacy analysis was the proportion of patients showing complete or partial response.

RESULTS: Seven patients were randomized to CBM and nine to placebo. Only one patient in the CBM arm was withdrawn due to AEs. A higher proportion of patients in the CBM group experienced a complete response during the overall observation period [5/7 (71.4%) with CMB vs. 2/9 (22.2%) with placebo, the difference being 49.2% (95% CI 1%, 75%)], due to the delayed period. The incidence of AEs was higher in the CBM group (86% vs. 67%). No serious AEs were reported. The mean daily dose was 4.8 sprays in both groups.

CONCLUSION: Compared with placebo, CBM added to standard antiemetic therapy was well tolerated and provided better protection against delayed CINV. These

results should be confirmed in a phase III clinical trial. 2010 Department of Health, Generalitat of Catalonia. British Journal of Clinical Pharmacology 2010 The British Pharmacological Society.

Fitzcharles, M.-A., et al. (2012). "Clinical implications for cannabinoid use in the rheumatic diseases: potential for help or harm?" Arthritis & Rheumatism **64**(8): 2417-2425.

Francis, H. (2011). "Emerging role of chronic cannabis usage and hyperemesis syndrome." Southern Medical Journal **104**(9): 665.

Frisardi, V., et al. (2011). "Glycerophospholipids and glycerophospholipid-derived lipid mediators: a complex meshwork in Alzheimer's disease pathology." Progress in Lipid Research **50**(4): 313-330.

An increasing body of evidence suggested that intracellular lipid metabolism is dramatically perturbed in various cardiovascular and neurodegenerative diseases with genetic and lifestyle components (e.g., dietary factors). Therefore, a lipidomic approach was also developed to suggest possible mechanisms underlying Alzheimer's disease (AD). Neural membranes contain several classes of glycerophospholipids (GPs), that not only constitute their backbone but also provide the membrane with a suitable environment, fluidity, and ion permeability. In this review article, we focused our attention on GP and GP-derived lipid mediators suggested to be involved in AD pathology. Degradation of GPs by phospholipase A(2) can release two important brain polyunsaturated fatty acids (PUFAs), e.g., arachidonic acid and docosahexaenoic acid, linked together by a delicate equilibrium. Non-enzymatic and enzymatic oxidation of these PUFAs produces several lipid mediators, all closely associated with neuronal pathways involved in AD neurobiology, suggesting that an interplay among lipids occurs in brain tissue. In this complex GP meshwork, the search for a specific modulating enzyme able to shift the metabolic pathway towards a neuroprotective role as well as a better knowledge about how lipid dietary modulation may act to slow the neurodegenerative processes, represent an essential step to delay the onset of AD and its progression. Also, in this way it may be possible to suggest new preventive or therapeutic options that can beneficially modify the course of this devastating disease. Copyright 2011 Elsevier Ltd. All rights reserved.

Furlow, B. (2012). "States and US Government spar over medical marijuana." Lancet Oncology **13**(5): 450.

Galli, J. A., et al. (2011). "Cannabinoid hyperemesis syndrome." Current Drug Abuse Reviews **4**(4): 241-249.

Coinciding with the increasing rates of cannabis abuse has been the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome. Cannabinoid Hyperemesis Syndrome is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing. Cannabinoid Hyperemesis Syndrome occurs by an unknown mechanism. Despite the well-

established anti-emetic properties of marijuana, there is increasing evidence of its paradoxical effects on the gastrointestinal tract and CNS. Tetrahydrocannabinol, cannabidiol, and cannabigerol are three cannabinoids found in the cannabis plant with opposing effects on the emesis response. The clinical course of Cannabinoid Hyperemesis Syndrome may be divided into three phases: prodromal, hyperemetic, and recovery phase. The hyperemetic phase usually ceases within 48 hours, and treatment involves supportive therapy with fluid resuscitation and anti-emetic medications. Patients often demonstrate the learned behavior of frequent hot bathing, which produces temporary cessation of nausea, vomiting, and abdominal pain. The broad differential diagnosis of nausea and vomiting often leads to delay in the diagnosis of Cannabinoid Hyperemesis Syndrome. Cyclic Vomiting Syndrome shares several similarities with CHS and the two conditions are often confused. Knowledge of the epidemiology, pathophysiology, and natural course of Cannabinoid Hyperemesis Syndrome is limited and requires further investigation.

Gerhardt, A., et al. (2012). "Subgroups of musculoskeletal pain patients and their psychobiological patterns - the LOGIN study protocol." BMC Musculoskeletal Disorders **13**: 136.

BACKGROUND: Pain conditions of the musculoskeletal system are very common and have tremendous socioeconomic impact. Despite its high prevalence, musculoskeletal pain remains poorly understood and predominantly non-specifically and insufficiently treated.The group of chronic musculoskeletal pain patients is supposed to be heterogeneous, due to a multitude of mechanisms involved in chronic pain. Psychological variables, psychophysiological processes, and neuroendocrine alterations are expected to be involved. Thus far, studies on musculoskeletal pain have predominantly focused on the general aspects of pain processing, thus neglecting the heterogeneity of patients with musculoskeletal pain. Consequently, there is a need for studies that comprise a multitude of mechanisms that are potentially involved in the chronicity and spread of pain. This need might foster research and facilitate a better pathophysiological understanding of the condition, thereby promoting the development of specific mechanism-based treatments for chronic pain. Therefore, the objectives of this study are as follows: 1) identify and describe subgroups of patients with musculoskeletal pain with regard to clinical manifestations (including mental co-morbidity) and 2) investigate whether distinct sensory profiles or 3) distinct plasma levels of pain-related parameters due to different underlying mechanisms can be distinguished in various subgroups of pain patients.

METHODS/DESIGN: We will examine a population-based chronic pain sample (n=100), a clinical tertiary care sample (n=100) and pain-free patients with depression or post-traumatic stress disorder and pain-free healthy controls (each n=30, respectively). The samples will be pain localisation matched by sex and age to the population-based sample. Patients will undergo physical examination and thorough assessments of mental co-morbidity (including psychological trauma), perceptual and central sensitisation (quantitative sensory testing), descending inhibition (conditioned pain modulation, the diffuse noxious inhibitory control-

like effect), as well as measurement of the plasma levels of nerve growth factor and endocannabinoids.

DISCUSSION: The identification of the underlying pathophysiologic mechanisms in different subgroups of chronic musculoskeletal pain patients will contribute to a mechanism-based subgroup classification. This will foster the development of mechanism-based treatments and holds promise to treat patients more sufficient.

Ghafouri, N., et al. (2011). "High levels of N-palmitoylethanolamide and N-stearoylethanolamide in microdialysate samples from myalgic trapezius muscle in women." PLoS ONE [Electronic Resource] **6**(11): e27257.

BACKGROUND: N-acylethanolamines (NAEs) are endogenous compounds that regulate inflammation and pain. These include the cannabinoid ligand anandamide (AEA) and the peroxisome proliferator-activated receptor- ligand palmitoylethanolamide (PEA). Little is known as to the levels of NAEs in pain states in human, particularly in the skeletal muscle. The aim of this study was to investigate the levels of these lipid mediators in muscle dialysate from women with chronic neck-/shoulder pain compared to healthy controls.

METHODS: Eleven women with chronic neck-/shoulder pain and eleven healthy women participated in this study. All participants went through microdialysis procedures in the trapezius muscle. Muscle dialysate samples were collected during four hours and analysed by nano liquid chromatography tandem mass spectrometry (nLC-MS/MS).

RESULTS: We were able to detect AEA, PEA, N-stearoylethanolamine (SEA) and 2-arachidonoylglycerol (2-AG) in a single chromatographic run. Of the NAEs studied, PEA and SEA were clearly detectable in the muscle microdialysate samples. The muscle dialysate levels of PEA and SEA were significantly higher in myalgic subjects compared to healthy controls.

CONCLUSION: This study demonstrates that microdialysis in combination with mass spectrometry can be used for analysing NAE's in human muscle tissue regularly over time. Furthermore the significant group differences in the concentration of PEA and SEA in this study might fill an important gap in our knowledge of mechanisms in chronic myalgia in humans. In the long run this expanded understanding of nociceptive and anitinociceptive processes in the muscle may provide a base for ameliorating treatment and rehabilitation of pain.

Gloss, D. and B. Vickrey (2012). "Cannabinoids for epilepsy." Cochrane Database of Systematic Reviews **6**: CD009270.

BACKGROUND: Marijuana appears to have anti-epileptic effects in animals. It is not currently known if it is effective in patients with epilepsy. Some states in the United States of America have explicitly approved its use for epilepsy.

OBJECTIVES: To assess the efficacy of marijuana, or one of marijuana's constituents in the treatment of people with epilepsy.

SEARCH METHODS: We searched the Cochrane Epilepsy Group Specialized Register (May 15, 2012), the Cochrane Central Register of Controlled Trials (CENTRAL issue 4 of 12, The Cochrane Library 2012),MEDLINE (PubMed, searched on May 15, 2012), ISI Web of Knowledge (May 15, 2012), CINAHL (EBSCOhost,

May 15, 2012), and ClinicalTrials.gov (May 15, 2012). In addition, we included studies we personally knew about that were not found by the searches, as well as references in the identified studies.

SELECTION CRITERIA: Randomized controlled trials (RCTs), whether blinded or not.

DATA COLLECTION AND ANALYSIS: Two authors independently selected trials for inclusion and extracted data. The primary outcome investigated was seizure freedom at one year or more, or three times the longest interseizure interval. Secondary outcomes included: responder rate at six months or more, objective quality of life data, and adverse events.

MAIN RESULTS: We found four randomized reports which included a total of 48 patients, each of which used cannabidiol as the treatment agent. One report was an abstract, and another was a letter to the editor. Anti-epileptic drugs were continued in all. Details of randomisation were not included in any study. There was no investigation of whether control and treatment groups were the same or different. All the reports were low quality.The four reports only answered the secondary outcome about adverse effects. None of the patients in the treatment groups suffered adverse effects.

AUTHORS' CONCLUSIONS: No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients, for generally short periods of time, and so the safety of long term cannabidiol treatment cannot be reliably assessed.

Goffin, K., et al. (2011). "In vivo activation of endocannabinoid system in temporal lobe epilepsy with hippocampal sclerosis." Brain **134**(Pt 4): 1033-1040.

The endocannabinoid system modulates neuronal excitability, protects neurons against hyperexcitability and is involved in epileptogenesis in animal models of mesial temporal lobe epilepsy with hippocampal sclerosis. We performed in vivo positron emission tomography imaging of the type 1 cannabinoid receptor in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Twelve patients with refractory mesial temporal lobe epilepsy due to hippocampal sclerosis received a [(18)F]MK-9470 scan to assess type 1 cannabinoid receptor availability in vivo. Parametric modified standard uptake values were used as quantitative measure of type 1 cannabinoid receptor availability and images were spatially normalized to standard space. Voxel-based analysis was performed comparing patients with hippocampal sclerosis to controls and correlations between type 1 cannabinoid receptor status and seizure characteristics were done using volumes of interest. Type 1 cannabinoid receptor positron emission tomography was co-registered with subtraction ictal single photon emission computed tomography co-registered to magnetic resonance imaging of a complex partial seizure (n=9). An increased type 1 cannabinoid receptor availability in the ipsilateral temporal lobe was observed, which correlated negatively with the latency since last seizure before scanning and positively to the number of seizures in the month before scanning. A decreased type 1 cannabinoid receptor availability was present in the superior insular cortex, ipsilateral more than contralateral. The ipsilateral insular region displayed a mild ictal hyperperfusion

in the transition zone of subtraction ictal single photon emission computed tomography co-registered to magnetic resonance imaging temporal lobe hyperperfusion-frontal lobe hypoperfusion during complex partial seizures. Type 1 cannabinoid receptor availability showed opposite changes in different brain regions that are involved during complex partial seizures in refractory mesial temporal lobe epilepsy with hippocampal sclerosis. The increase in type 1 cannabinoid receptor availability at the seizure onset zone might be a protective mechanism of neurons against hyperexcitability and seizure activity, or contribute to the process of epileptogenesis, or both. The decreased type 1 cannabinoid receptor availability in the insula may play a role in surround inhibition and prevention of seizure propagation.

Gowran, A., et al. (2011). "The multiplicity of action of cannabinoids: implications for treating neurodegeneration." CNS Neuroscience & Therapeutics **17**(6): 637-644.

The cannabinoid (CB) system is widespread in the central nervous system and is crucial for controlling a range of neurophysiological processes such as pain, appetite, and cognition. The endogenous CB molecules, anandamide, and 2-arachidonoyl glycerol, interact with the G-protein coupled CB receptors, CB(1) and CB(2). These receptors are also targets for the phytocannabinoids isolated from the cannabis plant and synthetic CB receptor ligands. The CB system is emerging as a key regulator of neuronal cell fate and is capable of conferring neuroprotection by the direct engagement of prosurvival pathways and the control of neurogenesis. Many neurological conditions feature a neurodegenerative component that is associated with excitotoxicity, oxidative stress, and neuroinflammation, and certain CB molecules have been demonstrated to inhibit these events to halt the progression of neurodegeneration. Such properties are attractive in the development of new strategies to treat neurodegenerative conditions of diverse etiology, such as Alzheimer's disease, multiple sclerosis, and cerebral ischemia. This article will discuss the experimental and clinical evidence supporting a potential role for CB-based therapies in the treatment of certain neurological diseases that feature a neurodegenerative component. 2010 Blackwell Publishing Ltd.

Green, A. J. and K. De-Vries (2010). "Cannabis use in palliative care - an examination of the evidence and the implications for nurses." Journal of Clinical Nursing **19**(17-18): 2454-2462.

AIM AND OBJECTIVE: Examine the pharmaceutical qualities of cannabis including a historical overview of cannabis use. Discuss the use of cannabis as a clinical intervention for people experiencing palliative care, including those with life-threatening chronic illness such as multiple sclerosis and motor neurone disease [amyotrophic lateral sclerosis] in the UK.

BACKGROUND: The non-medicinal use of cannabis has been well documented in the media. There is a growing scientific literature on the benefits of cannabis in symptom management in cancer care. Service users, nurses and carers need to be aware of the implications for care and treatment if cannabis is being used medicinally.

DESIGN: A comprehensive literature review.
METHOD: Literature searches were made of databases from 1996 using the term cannabis and the combination terms of cannabis and palliative care; symptom management; cancer; oncology; chronic illness; motor neurone disease/amyotrophic lateral sclerosis; and multiple sclerosis. Internet material provided for service users searching for information about the medicinal use of cannabis was also examined.
RESULTS: The literature on the use of cannabis in health care repeatedly refers to changes for users that may be equated with improvement in quality of life as an outcome of its use. This has led to increased use of cannabis by these service users. However, the cannabis used is usually obtained illegally and can have consequences for those who choose to use it for its therapeutic value and for nurses who are providing care.
RELEVANCE TO CLINICAL PRACTICE: Questions and dilemmas are raised concerning the role of the nurse when caring and supporting a person making therapeutic use of cannabis. 2010 Blackwell Publishing Ltd.

Greenwell, G. T. (2012). "Medical marijuana use for chronic pain: risks and benefits." Journal of Pain & Palliative Care Pharmacotherapy **26**(1): 68-69.

Questions from patients about medical marijuana use for chronic pain are becoming more common. The information in this report will help patients understand the potential risks and benefits of using this substance for painful conditions.

Group, A. L. (2012). "ALSUntangled No. 16: cannabis." Amyotrophic Lateral Sclerosis **13**(4): 400-404.

Guindon, J. (2012). "Nabilone in inflammatory pain: to be or not to be." Clinical & Experimental Pharmacology & Physiology **39**(4): 327-328.

Hanlon, K. E. and T. W. Vanderah (2010). "Constitutive activity at the cannabinoid CB(1) receptor and behavioral responses." Methods in Enzymology **484**: 3-30.

The cannabinoid receptor type 1, found mainly on cells of the central and peripheral nervous system, is a major component of the endogenous cannabinoid system. Constitutive and endogenous activity at cannabinoid receptor type 1 regulates a diverse subset of biological processes including appetite, mood, motor function, learning and memory, and pain. The complexity of cannabinoid receptor type 1 activity is not limited to the constitutive activity of the receptor: promiscuity of ligands associated with and the capability of this receptor to instigate G protein sequestration also complicates the activity of cannabinoid receptor type 1. The therapeutic use of cannabinoid receptor type 1 agonists is still a heavily debated topic, making research on the mechanisms underlying the potential benefits and risks of cannabinoid use more vital than ever. Elucidation of these mechanisms and the quest for agonists and antagonists with greater specificity will allow a greater control of the side effects and risks involved in utilizing cannabinoids as therapeutic agents. In this chapter, we review a small

subset of techniques used in the pharmacological application of and the behavioral effects of molecules acting at the paradoxical cannabinoid receptor type 1. Copyright 2010 Elsevier Inc. All rights reserved.

Hasan, A., et al. (2010). "Oral delta 9-tetrahydrocannabinol improved refractory Gilles de la Tourette syndrome in an adolescent by increasing intracortical inhibition: a case report." Journal of Clinical Psychopharmacology **30**(2): 190-192.

OBJECTIVE: To describe the clinical course of the Delta 9-tetrahydrocannabinol (Delta 9-THC) treatment of a boy with Gilles de la Tourette Syndrome (TS) and comorbid attention-deficit/hyperactivity disorder (ADHD) in relation to Delta 9-THC plasma levels and intracortical inhibition measured by transcranial magnetic stimulation.

METHODS: The clinical course and pharmacological and neurophysiological measures are reported in a 15-year-old boy with treatment refractory TS plus ADHD leading to severe physical and psychosocial impairment.

RESULTS: Administration of Delta 9-THC improved tics considerably without adverse effects, allowing parallel stimulant treatment of comorbid ADHD. Along with the Delta 9-THC treatment, intracortical inhibition was increased, reflected in the enhanced short-interval intracortical inhibition and the prolongation of the cortical silent period.

CONCLUSIONS: Our observation suggests that Delta 9-THC might be a successful alternative in patients with severe TS refractory to classic treatment. Particularly in the case of stimulant-induced exacerbation of tics, Delta 9-THC might enable successful treatment of comorbid ADHD. The enhancement of intracortical inhibition might be mediated by modulating release of several neurotransmitters including dopamine and gamma-aminobutyric acid. Further studies are needed to substantiate our findings.

Hesselink, J. M. K. and D. J. Kopsky (2011). "Enhancing acupuncture by low dose naltrexone." Acupuncture in Medicine **29**(2): 127-130.

To find appropriate and effective treatment options for chronic pain syndromes is a challenging task. Multimodal treatment approach has been gaining acceptance for chronic pain. However, combining treatments, such as acupuncture, with rational pharmacology is still in its infancy. Acupuncture influences the opioid and cannabinoid system through releasing endogenous receptor ligands. Low dose naltrexone also acts on both these systems, and upregulates the opioid and cannabinoid receptors. The authors hypothesise that low dose naltrexone could enhance the pain-relieving effect of acupuncture.

Hesselink, J. M. K. and D. J. Kopsky (2012). "Intractable neuropathic pain due to ulnar nerve entrapment treated with cannabis and ketamine 10%." Journal of Clinical Anesthesia **24**(1): 78-79.

Hogan, J., et al. (2010). "Pain-related anxiety and marijuana use motives: a pilot test among active marijuana-using young adults." Cognitive Behaviour Therapy **39**(4): 283-292.

The present investigation examined pain-related anxiety in regard to marijuana use motives among a sample of young adult marijuana users (N = 180; 45% women; M(age) = 21.11 years, SD = 6.41). Hierarchical multiple regression analyses were used to determine the relations between pain-related anxiety and marijuana use motives. After controlling for current marijuana use frequency (past 30 days), daily cigarette smoking rate, current rate of alcohol consumption, level of bodily pain (current), and other marijuana use motives, pain-related anxiety was significantly and uniquely associated with coping and conformity motives for marijuana use. Pain-related anxiety was not significantly related to other marijuana use motives. These results offer novel empirical insight pertaining to a relation between pain-related anxiety and coping as well as conformity motives for marijuana use among active users.

Honarmand, K., et al. (2011). "Effects of cannabis on cognitive function in patients with multiple sclerosis." Neurology **76**(13): 1153-1160.

BACKGROUND: While neuropsychological deficits have been reported in healthy individuals who use street cannabis, data in patients with multiple sclerosis (MS) are lacking. Given that MS is associated with cognitive deterioration, the aim of this study was to determine the neuropsychological effects of cannabis use in this population.

METHODS: Two groups, each of 25 patients with MS (cannabis users and nonusers), were administered the Minimal Assessment of Cognitive Function in MS battery of neuropsychological tests, the Hospital Anxiety and Depression Scale (HADS), and the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Group-matching and regression analysis were used to control for the effects of age, sex, education, premorbid intelligence, disability, and disease course and duration on cognitive function.

RESULTS: Cannabis users performed significantly more poorly than nonusers on measures of information processing speed, working memory, executive functions, and visuospatial perception. They were also twice as likely as nonusers to be classified as globally cognitively impaired. There were no between-group differences on the HADS measures of depression and anxiety or lifetime SCID-I psychiatric diagnoses.

CONCLUSION: This cross-sectional study provides empirical evidence that prolonged use of inhaled or ingested street cannabis in patients with MS is associated with poorer performance on cognitive domains commonly affected in this population. Whatever subjective benefits patients may derive from using street cannabis (e.g., pain and spasticity relief) should be weighed against the associated cognitive side effects.

Huestis, M. A., et al. (2011). "Oral fluid testing: promises and pitfalls." Clinical Chemistry **57**(6): 805-810.

Huggins, J. P., et al. (2012). "An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain

due to osteoarthritis of the knee." Pain **153**(9): 1837-1846.

The effect of PF-04457845, a potent and selective fatty acid amide hydrolase-1 (FAAH1) inhibitor, on pain due to osteoarthritis of the knee was investigated in a randomised placebo and active-controlled clinical trial. The trial involved 2 periods (separated by a 2-week washout) consisting of a 1-week wash-in phase followed by 2weeks double-blind treatment. Patients received single-blind placebo throughout the wash-in and washout periods. Patients were randomised to receive either 4mg q.d. PF-04457845 followed by placebo (or vice versa), or 500mg b.i.d. naproxen followed by placebo (or vice versa). The primary end point was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. The trial had predefined decision rules based on likelihood that PF-04457845 was better or worse than the standard of care (considered to be a 1.8 reduction in WOMAC pain score compared to placebo). A total of 74 patients were randomised to 1 of 4 treatment sequences. The mean differences (80% confidence intervals) from placebo in WOMAC pain score were 0.04 (-0.63 to 0.71) for PF-04457845 and -1.13 (-1.79 to -0.47) for naproxen, indicating that whilst naproxen seemed efficacious, PF-04457845 was not differentiated from placebo. The study was stopped at the interim analysis for futility. PF-04457845 decreased FAAH activity by >96% and substantially increased 4 endogenous substrates (fatty acid amides). PF-04457845 was well tolerated in osteoarthritis patients, and there was no evidence of cannabinoid-type adverse events. The lack of analgesic effect of FAAH1 inhibition in humans is in contrast to data from animal models. This apparent disconnect between species needs further study. 

Jung, K.-M., et al. (2012). "An amyloid 42-dependent deficit in anandamide mobilization is associated with cognitive dysfunction in Alzheimer's disease." Neurobiology of Aging **33**(8): 1522-1532.

The endocannabinoids and their attending cannabinoid (CB)(1) receptors have been implicated in the control of cognition, but their possible roles in dementias are still unclear. In the present study, we used liquid chromatography/mass spectrometry to conduct an endocannabinoid-targeted lipidomic analysis of postmortem brain samples from 38 Alzheimer's disease (AD) patients and 17 control subjects, matched for age and postmortem interval. The analysis revealed that midfrontal and temporal cortex tissue from AD patients contains, relative to control subjects, significantly lower levels of the endocannabinoid anandamide and its precursor 1-stearoyl, 2-docosahexaenoyl-sn-glycero-phosphoethanolamine-N-arachidonoyl (NArPE). No such difference was observed with the endocannabinoid 2-arachidonoyl-sn-glycerol or 15 additional lipid species. In AD patients, but not in control subjects, statistically detectable positive correlations were found between (1) anandamide content in midfrontal cortex and scores of the Kendrick's Digit Copy test ($p = 0.004$, $r = 0.81$; $n = 10$), which measures speed of information processing; and (2) anandamide content in temporal cortex and scores of the Boston Naming test ($p = 0.027$, $r = 0.52$; $n = 18$), which assesses language facility. Furthermore, anandamide and NArPE

levels in midfrontal cortex of the study subjects inversely correlated with levels of the neurotoxic amyloid peptide, amyloid -protein (A)(42), while showing no association with A(40) levels, amyloid plaque load or tau protein phosphorylation. Finally, high endogenous levels of A(42) in Swedish mutant form of amyloid precursor protein (APP(SWE))/Neuro-2a cells directly reduced anandamide and NArPE concentrations in cells lysates. The results suggest that an A(42)-dependent impairment in brain anandamide mobilization contributes to cognitive dysfunction in AD. 

Kalliomaki, J., et al. (2012). "Lack of effect of central nervous system-active doses of nabilone on capsaicin-induced pain and hyperalgesia." Clinical & Experimental Pharmacology & Physiology **39**(4): 336-342.

The aim of the present study was to investigate the effects of nabilone on capsaicin-induced pain and hyperalgesia, as well as on biomarkers of cannabinoid central nervous system (CNS) effects. A randomized, double-blind, placebo-controlled, crossover study was conducted in 30 healthy male volunteers receiving single doses of nabilone (1, 2 or 3mg). Pain intensity after intradermal capsaicin injections in the forearm was assessed by continuous visual analogue scale (0-100mm). Capsaicin cream was applied to the calf to induce hyperalgesia. Primary hyperalgesia was assessed by measuring heat pain thresholds, whereas secondary hyperalgesia was assessed by measuring the area where light tactile stimulation was felt to be painful. Pain and hyperalgesia were measured at baseline and 2-3.5h after dosing. The CNS effects were assessed at baseline and up to 24h after dosing using visual analogue mood scales for feeling 'stimulated', 'anxious', 'sedated' and 'down'. Plasma samples for pharmacokinetic analysis were obtained up to 24h after drug administration. Nabilone did not significantly attenuate either ongoing pain or primary or secondary hyperalgesia, whereas dose-dependent CNS effects were observed from 1.5 to 6h after dosing, being maximal at 4-6h. Plasma concentrations of nabilone and its metabolite carbinol were maximal 1-2h after dosing. Adverse events (AE) were common on nabilone treatment. Four subjects withdrew due to pronounced CNS AE (anxiety, agitation, altered perception, impaired consciousness). Although nabilone had marked CNS effects, no analgesic or antihyperalgesic effects were observed. 

Kamat, A. S., et al. (2012). "Headache after substance abuse: a diagnostic dilemma." Journal of Clinical Neuroscience **19**(3): 464-466.

An 18-year-old man inhaled a substance containing synthetic cannabinoids and 1 hour later developed a severe global headache. Imaging revealed a perimesencephalic subarachnoid haemorrhage. An angiogram suggested that a small superior cerebellar artery aneurysm was the culprit. This report discusses the, as yet undefined, relationship between "herbal highs" and intracranial haemorrhage. 

Karl, T., et al. (2012). "The therapeutic potential of the endocannabinoid system for

Alzheimer's disease." Expert Opinion on Therapeutic Targets **16**(4): 407-420.
INTRODUCTION: Dementia currently affects over 35 million people worldwide. The most common form of dementia is Alzheimer's disease (AD). Currently, treatments for AD do not stop or reverse the progression of the disease and they are accompanied by side effects. AREAS COVERED: The main features of AD pathology, treatment options currently available, the endocannabinoid system and its functionality in general and its role in AD pathology in detail will be outlined. A particular focus will be on the therapeutic potential of the phytocannabinoid cannabidiol. EXPERT OPINION: Based on the complex pathology of AD, a preventative, multimodal drug approach targeting a combination of pathological AD symptoms appears ideal. Importantly, cannabinoids show anti-inflammatory, neuroprotective and antioxidant properties and have immunosuppressive effects. Thus, the cannabinoid system should be a prime target for AD therapy. The cannabinoid receptor 2 appears to be a promising candidate but its role in AD has to be investigated cautiously. Furthermore, the phytocannabinoid cannabidiol is of particular interest as it lacks the psychoactive and cognition-impairing properties of other cannabinoids. In conclusion, future research should focus on the evaluation of the effects of manipulations to the endocannabinoid system in established animal models for AD, combined with early-phase studies in humans.

Karst, M., et al. (2010). "Role of cannabinoids in the treatment of pain and (painful) spasticity." Drugs **70**(18): 2409-2438.
Both the discovery of the endocannabinoid system (ECS) and its role in the control of pain and habituation to stress, as well as the significant analgesic and antihyperalgesic effects in animal studies, suggest the usefulness of cannabinoids in pain conditions. However, in human experimental or clinical trials, no convincing reduction of acute pain, which may be caused by a pronociceptive, ECS-triggered mechanism on the level of the spinal cord, has been demonstrated. In contrast, in chronic pain and (painful) spasticity, an increasing number of randomized, double-blind, placebo-controlled studies have shown the efficacy of cannabinoids, which is combined with a narrow therapeutic index. Patients with unsatisfactory response to other methods of pain therapy and who were characterized by failed stress adaptation particularly benefited from treatment with cannabinoids. None of the attempts to overcome the disadvantage of the narrow therapeutic index, either by changing the route of application or by formulating balanced cannabinoid preparations, have resulted in a major breakthrough. Therefore, different methods of administration and other types of cannabinoids, such as endocannabinoid modulators, should be tested in future trials.

Kiferle, L., et al. (2011). "Positron emission tomography imaging in multiple sclerosis-current status and future applications." European Journal of Neurology **18**(2): 226-231.
BACKGROUND: Multiple Sclerosis (MS) is traditionally considered as a central nervous system (CNS) white matter inflammatory disease. However, recent studies have focused on the neurodegenerative aspects of the disease, which occur early in the pathological process, providing an opportunity for therapeutic

intervention and application of neuroprotective strategies. The relationship between neural inflammation and cell death remains controversial. The recent development of new radiolabelled ligands provides positron emission tomography (PET) imaging with a role for studying early aspects of the MS pathology.
METHODS: We provide an overview of current PET research in MS, particularly focussing on possible applications of new radioligands for studying inflammation and neurodegenerative processes.
RESULTS: Pathological aspects of neuroinflammation, axonal degeneration and neuronal repair may be explored in vivo with selective PET tracers. Specific radioligands for the cannabinoid system may be applied in MS research to understand the role of this neurotransmitter system in the pathogenesis of the disease.
CONCLUSIONS: PET imaging represents a promising tool for elucidating controversial aspects of MS pathology and for the assessment of selective and potentially neuroprotective therapies. 2010 The Author(s). European Journal of Neurology 2010 EFNS.

Kirkham, T. C. (2009). "Endocannabinoids and the non-homeostatic control of appetite." Current Topics in Behavioral Neurosciences **1**: 231-253.
The usual physiological perspective on appetite and food intake regards control of eating simplistically, as merely the reflexive behavioural component of a strict homeostatic regulatory system. Hunger is seen to arise in response to energy deficit; meal size is determined by the passage of nutrients into the gut and the stimulation of multiple satiety signals; and overall energy intake is modified to reflect the balance of fuel reserves and energy expenditure. But everyday experience shows that we rarely eat simply through need. Rather, food stimuli exert a powerful influence over consumption through their appeal to innate and learned appetites, generating the psychological experiences of hunger, craving and delight independently of energy status. That these important and influential subjective experiences are mediated through complex neurochemical processes is self-evident; but the chemical nature of our infatuation with, and subservience to, the motivating properties of foods are overshadowed by mechanistic, peripherally anchored models that take little account of psychological factors, and which consequently struggle to explain the phenomenon of obesity. This chapter discusses recent developments that suggest the endocannabinoids are key components of the central mechanisms that give rise to the emotional and motivational experiences that lead us to eat and to overconsume.

Klooker, T. K., et al. (2011). "The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients." Neurogastroenterology & Motility **23**(1): 30-35.
BACKGROUND: Visceral hypersensitivity to distension is thought to play an important role in the pathophysiology of the irritable bowel syndrome (IBS). Cannabinoids are known to decrease somatic pain perception, but their effect on visceral sensitivity in IBS remains unclear. Therefore, we evaluated the effect of the mixed CB(1) /CB(2) receptor agonist delta-9-tetrahydrocannabinol ((9) -THC,

dronabinol) on rectal sensitivity.

METHODS: Ten IBS patients and 12 healthy volunteers (HV) underwent a barostat study to assess rectal sensitivity using an intermittent pressure-controlled distension protocol before and after sigmoid stimulation. Repetitive sigmoid stimulation is a validated method to increase visceral perception in IBS patients, consisting of a 10-min period of 30 s stimuli (60 mmHg), separated by 30 s of rest (5 mmHg). The effect of placebo and (9) -THC (5 and 10 mg in healthy volunteers and 10 mg in IBS patients) on rectal sensitivity was evaluated on respectively three and two separate days in a double blind, randomized, crossover fashion.

KEY RESULTS: All participants (HV and IBS) reported central side effects during the highest dose of (9) -THC, most frequently increased awareness of the surrounding, light-headedness and sleepiness, whereas no side effects where reported during placebo. Although blood pressure was not affected, heart rate increased in both HV and IBS, but was most pronounced in IBS patients. The cannabinoid agonist (9) -THC did not alter baseline rectal perception to distension compared to placebo in HV or IBS patients. Similarly, after sigmoid stimulation there were no significant differences between placebo and (9) -THC in sensory thresholds of discomfort.

CONCLUSIONS & INFERENCES: These findings imply that (9) -THC does not modify visceral perception to rectal distension and argue against (centrally acting) CB agonists as tool to decrease visceral hypersensitivity in IBS patients. 2010 Blackwell Publishing Ltd.

Klumpers, L. E., et al. (2012). "Novel (9) -tetrahydrocannabinol formulation Namisol has beneficial pharmacokinetics and promising pharmacodynamic effects." British Journal of Clinical Pharmacology **74**(1): 42-53.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT: * Cannabis based medicines are registered as a treatment for various indications, such as pain and spasms in multiple sclerosis (MS) patients, and anorexia and nausea in patients with HIV or receiving cancer treatment. * the pharmacokinetics of the various administration routes of cannabis and cannabis based medicines are variable and dosing is hard to regulate.

WHAT THIS STUDY ADDS: * Namisol is a new tablet containing pure THC (>98%) that has a beneficial pharmacokinetic profile after oral administration. * Namisol gives a quick onset of pharmacodynamic effects in healthy volunteers, which implies a rapid initiation of therapeutic effects in patients.

AIMS: Among the main disadvantages of currently available (9) -tetrahydrocannabinol (THC) formulations are dosing difficulties due to poor pharmacokinetic characteristics. Namisol is a novel THC formulation, designed to improve THC absorption. The study objectives were to investigate the optimal administration route, pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of Namisol.

METHODS: This first in human study consisted of two parts. Panel I included healthy males and females (n = 6/6) in a double-blind, double-dummy, randomized, crossover study with sublingual (crushed tablet) and oral administration of Namisol (5 mg THC). Based on these results, male and female (n = 4/5)

participants from panel I received oral THC 6.5 and 8.0 mg or matching placebo in a randomized, crossover, rising dose study during panel II. PD measurements were body sway; visual analogue scales (VAS) mood, psychedelic and heart rate. THC and 11-OH-THC population PK analysis was performed.

RESULTS: Sublingual administration showed a flat concentration profile compared with oral administration. Oral THC apparent t(1/2) was 72-80 min, t(max) was 39-56 min and C(max) 2.92-4.69 ng ml(-1) . THC affected body sway (60.8%, 95% CI 29.5, 99.8), external perception (0.078 log mm, 95% CI 0.019, 0.137), alertness (-2.7 mm, 95% CI -4.5, -0.9) feeling high (0.256 log mm, 95% CI 0.093, 0.418) and heart rate (5.6 beats min(-1) , 95% CI 2.7, 6.5). Namisol was well tolerated.

CONCLUSIONS: Oral Namisol showed promising PK and PD characteristics. Variability and t(max) of THC plasma concentrations were smaller for Namisol than reported for studies using oral dronabinol and nabilone. This study was performed in a limited number of healthy volunteers. Therefore, future research on Namisol should study clinical effects in patient populations. 2011 The Authors. British Journal of Clinical Pharmacology 2011 The British Pharmacological Society.

Kopsky, D. J. and J. M. K. Hesselink (2010). "Nerve regeneration in neuropathic pain." Pain Medicine **11**(10): 1576.

Kopsky, D. J. and J. M. K. Hesselink (2012). "Multimodal stepped care approach with acupuncture and PPAR- agonist palmitoylethanolamide in the treatment of a patient with multiple sclerosis and central neuropathic pain." Acupuncture in Medicine **30**(1): 53-55.

Central neuropathic pain is a common debilitating symptom in patients with multiple sclerosis. Side effects of analgesics often limit reaching therapeutic dosages. In this case report, a 61-year-old woman with chronic central neuropathic pain due to multiple sclerosis is described. Acupuncture could only partly and temporarily reduce the pain. However, after adding the natural compound palmitoylethanolamide, a glial modulator and peroxisome proliferator-activated receptor- agonist, pain reduction was more pronounced and the interval between acupuncture sessions could be increased. A multimodal stepped care approach is demonstrated, with acupuncture and palmitoylethanolamide both influencing non-neuronal cells, such as activated glial cells, which are key factors in the development and maintenance of neuropathic pain.

Kovacs, F. E., et al. (2012). "Exogenous and endogenous cannabinoids suppress inhibitory neurotransmission in the human neocortex." Neuropsychopharmacology **37**(5): 1104-1114.

Activation of CB(1) receptors on axon terminals by exogenous cannabinoids (eg, (9)-tetrahydrocannabinol) and by endogenous cannabinoids (endocannabinoids) released by postsynaptic neurons leads to presynaptic inhibition of neurotransmission. The aim of this study was to characterize the effect of cannabinoids on GABAergic synaptic transmission in the human neocortex. Brain slices were prepared from neocortical tissues surgically removed to eliminate epileptogenic foci. Spontaneous GABAergic inhibitory postsynaptic currents

(sIPSCs) were recorded in putative pyramidal neurons using patch-clamp techniques. To enhance the activity of cannabinoid-sensitive presynaptic axons, muscarinic receptors were continuously stimulated by carbachol. The synthetic cannabinoid receptor agonist WIN55212-2 decreased the cumulative amplitude of sIPSCs. The CB(1) antagonist rimonabant prevented this effect, verifying the involvement of CB(1) receptors. WIN55212-2 decreased the frequency of miniature IPSCs (mIPSCs) recorded in the presence of tetrodotoxin, but did not change their amplitude, indicating that the neurotransmission was inhibited presynaptically. Depolarization of postsynaptic pyramidal neurons induced a suppression of sIPSCs. As rimonabant prevented this suppression, it is very likely that it was due to endocannabinods acting on CB(1) receptors. This is the first demonstration that an exogenous cannabinoid inhibits synaptic transmission in the human neocortex and that endocannabinoids released by postsynaptic neurons suppress synaptic transmission in the human brain. Interferences of cannabinoid agonists and antagonists with synaptic transmission in the cortex may explain the cognitive and memory deficits elicited by these drugs.

Kraft, B. (2012). "Is there any clinically relevant cannabinoid-induced analgesia?" Pharmacology **89**(5-6): 237-246.

Lamarine, R. J. (2012). "Marijuana: modern medical chimaera." Journal of Drug Education **42**(1): 1-11.

Marijuana has been used medically since antiquity. In recent years there has been a resurgence of interest in medical applications of various cannabis preparations. These drugs have been cited in the medical literature as potential secondary treatment agents for severe pain, muscle spasticity, anorexia, nausea, sleep disturbances, and numerous other uses. This article reviews the research literature related to medical applications of various forms of cannabis. Benefits related to medical use of cannabinoids are examined and a number of potential risks associated with cannabis use, both medical and recreational, are considered. There is a clearly identified need for further research to isolate significant benefits from the medical application of cannabinoids and to establish dosage levels, appropriate delivery mechanisms and formulations, and to determine what role, if any, cannabinoids might play in legitimate medical applications. It is also imperative to determine if reported dangers pose a significant health risks to users.

Lapoint, J., et al. (2011). "Severe toxicity following synthetic cannabinoid ingestion." Clinical Toxicology: The Official Journal of the American Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists **49**(8): 760-764.

OBJECTIVE: To report a case of seizures and supraventricular tachycardia (SVT) following confirmed synthetic cannabinoid ingestion.

BACKGROUND: Despite widespread use of legal synthetic cannabinoids, reports of serious toxicity following confirmed use of synthetic cannabinoids are rare. We report severe toxicity including seizures following intentional ingestion of the

synthetic cannabinoid JWH-018 and detail confirmation by laboratory analysis.
CASE REPORT: A healthy 48 year old man had a generalized seizure within thirty minutes of ingesting an ethanol mixture containing a white powder he purchased from the Internet in an attempt to get high. Seizures recurred and abated with lorazepam. Initial vital signs were: pulse, 106/min; BP, 140/88 mmHg; respirations, 22/min; temperature, 37.7 C. A noncontrast computed tomography of the brain and EEG were negative, and serum chemistry values were normal. The blood ethanol concentration was 3.8 mg/dL and the CPK 2,649 U/L. Urine drug screening by EMIT was negative for common drugs of abuse, including tetrahydrocannabinol. On hospital day 1, he developed medically refractory SVT. The patient had no further complications and was discharged in his normal state of health 10 days after admission. The original powder was confirmed by gas chromatography mass spectrometry to be JWH-018, and a primary JWH-018 metabolite was detected in the patient's urine (200 nM) using liquid chromatography tandem mass spectrometry.
DISCUSSION: Synthetic cannabinoids are legal in many parts of the world and easily obtained over the Internet. Data on human toxicity are limited and real-time confirmatory testing is unavailable to clinicians. The potential for toxicity exists for users mistakenly associating the dose and side effect profiles of synthetic cannabinoids to those of marijuana.
CONCLUSION: Ingestion of JWH-018 can produce seizures and tachyarrhythmias. Clinicians, lawmakers, and the general public need to be aware of the potential for toxicity associated with synthetic cannabinoid use.

Leung, L. (2011). "Cannabis and its derivatives: review of medical use." Journal of the American Board of Family Medicine: JABFM **24**(4): 452-462.
BACKGROUND: Use of cannabis is often an under-reported activity in our society. Despite legal restriction, cannabis is often used to relieve chronic and neuropathic pain, and it carries psychotropic and physical adverse effects with a propensity for addiction. This article aims to update the current knowledge and evidence of using cannabis and its derivatives with a view to the sociolegal context and perspectives for future research.
METHODS: Cannabis use can be traced back to ancient cultures and still continues in our present society despite legal curtailment. The active ingredient, 9-tetrahydrocannabinol, accounts for both the physical and psychotropic effects of cannabis. Though clinical trials demonstrate benefits in alleviating chronic and neuropathic pain, there is also significant potential physical and psychotropic side-effects of cannabis. Recent laboratory data highlight synergistic interactions between cannabinoid and opioid receptors, with potential reduction of drug-seeking behavior and opiate sparing effects. Legal rulings also have changed in certain American states, which may lead to wider use of cannabis among eligible persons.
CONCLUSIONS: Family physicians need to be cognizant of such changing landscapes with a practical knowledge on the pros and cons of medical marijuana, the legal implications of its use, and possible developments in the future.

Little, J. P., et al. (2011). "Therapeutic potential of cannabinoids in the treatment of neuroinflammation associated with Parkinson's disease." Mini-Reviews in Medicinal Chemistry **11**(7): 582-590.

The cannabinoid system is represented by two principal receptor subtypes, termed CB1 and CB2, along with several endogenous ligands. In the central nervous system it is involved in several processes. CB1 receptors are mainly expressed by neurons and their activation is primarily implicated in psychotropic and motor effects of cannabinoids. CB2 receptors are expressed by glial cells and are thought to participate in regulation of neuroimmune reactions. This review aims to highlight several reported properties of cannabinoids that could be used to inhibit the adverse neuroinflammatory processes contributing to Parkinson's disease and possibly other neurodegenerative disorders. These include anti-oxidant properties of phytocannabinoids and synthetic cannabinoids as well as hypothermic and antipyretic effects. However, cannabinoids may also trigger signaling cascades leading to impaired mitochondrial enzyme activity, reduced mitochondrial biogenesis, and increased oxidative stress, all of which could contribute to neurotoxicity. Therefore, further pharmacological studies are needed to allow rational design of new cannabinoid-based drugs lacking detrimental in vivo effects.

Lucas, P. (2012). "Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain." Journal of Psychoactive Drugs **44**(2): 125-133.

There is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates in the treatment of chronic pain. When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting. Additionally, cannabinoids can prevent the development of tolerance to and withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective. Novel research suggests that cannabis may be useful in the treatment of problematic substance use. These findings suggest that increasing safe access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the growing problematic use of pharmaceutical opiates. Despite a lack of regulatory oversight by federal governments in North America, community-based medical cannabis dispensaries have proven successful at supplying patients with a safe source of cannabis within an environment conducive to healing, and may be reducing the problematic use of pharmaceutical opiates and other potentially harmful substances in their communities.

Luther, V. and L. Yap (2012). "A hot bath to calm what ails you: the Cannabis Hyperemesis Syndrome." Acute Medicine **11**(1): 23-24.

The Cannabis Hyperemesis Syndrome (CHS) defines a recently described paradoxical association between recurrent vomiting episodes, daily cannabis excess and symptomatic relief with a hot bath or shower. Importantly, symptom resolution only occurs with cessation of cannabis use. We describe a case of CHS which had resulted in repeated hospital admissions. As cannabis use is common, it

is important for both patients and Acute Physicians to be aware of this increasingly recognised condition.

Lynch, M. E. and F. Campbell (2011). "Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials." British Journal of Clinical Pharmacology **72**(5): 735-744.

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. 2011 The Authors. British Journal of Clinical Pharmacology 2011 The British Pharmacological Society.

Marini, I., et al. (2012). "Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain." Journal of Orofacial Pain **26**(2): 99-104.

AIMS: To carry out a randomized clinical trial to compare the effect of palmitoylethanolamide (PEA) versus ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), for pain relief in temporomandibular joint (TMJ) osteoarthritis or arthralgia. PEA acts as an endogenous agent with an autacoid local inflammation antagonism and modulates mast cell behavior controlling both acute and chronic inflammation.

METHODS: A triple-blind randomized clinical trial was conducted on 24 patients (16 women and 8 men) aged 24 to 54 years and suffering from TMJ osteoarthritis or arthralgia. The patients were enrolled from a group of 120 consecutive patients referred to the University of Bologna's Department of Orthodontics. Patients were randomly divided into two groups: group A (12 subjects) received PEA 300 mg in the morning and 600 mg in the evening for 7 days and then 300 mg twice a day for 7 more days. Group B (12 subjects) received ibuprofen 600 mg three times a day for 2 weeks. Every patient recorded the intensity of spontaneous pain on a visual analog scale twice a day. Maximum mouth opening was recorded by a

blind operator during the first visit and again after the 14th day of drug treatment. A t test was used for data comparisons. Results: Pain decrease after 2 weeks of treatment was significantly higher in group A than in group B (P = .0001); maximum mouth opening improved more in group A than in group B (P = .022).
CONCLUSION: These data suggest that PEA is effective in treating TMJ inflammatory pain.

Martin-Moreno, A. M., et al. (2012). "Prolonged oral cannabinoid administration prevents neuroinflammation, lowers -amyloid levels and improves cognitive performance in Tg APP 2576 mice." Journal of Neuroinflammation **9**: 8.

BACKGROUND: Alzheimer's disease (AD) brain shows an ongoing inflammatory condition and non-steroidal anti-inflammatories diminish the risk of suffering the neurologic disease. Cannabinoids are neuroprotective and anti-inflammatory agents with therapeutic potential.
METHODS: We have studied the effects of prolonged oral administration of transgenic amyloid precursor protein (APP) mice with two pharmacologically different cannabinoids (WIN 55,212-2 and JWH-133, 0.2 mg/kg/day in the drinking water during 4 months) on inflammatory and cognitive parameters, and on 18F-fluoro-deoxyglucose (18FDG) uptake by positron emission tomography (PET).
RESULTS: Novel object recognition was significantly reduced in 11 month old Tg APP mice and 4 month administration of JWH was able to normalize this cognitive deficit, although WIN was ineffective. Wild type mice cognitive performance was unaltered by cannabinoid administration. Tg APP mice showed decreased 18FDG uptake in hippocampus and cortical regions, which was counteracted by oral JWH treatment. Hippocampal GFAP immunoreactivity and cortical protein expression was unaffected by genotype or treatment. In contrast, the density of Iba1 positive microglia was increased in Tg APP mice, and normalized following JWH chronic treatment. Both cannabinoids were effective at reducing the enhancement of COX-2 protein levels and TNF- mRNA expression found in the AD model. Increased cortical -amyloid (A) levels were significantly reduced in the mouse model by both cannabinoids. Noteworthy both cannabinoids enhanced A transport across choroid plexus cells in vitro.
CONCLUSIONS: In summary we have shown that chronically administered cannabinoid showed marked beneficial effects concomitant with inflammation reduction and increased A clearance.

Martin-Moreno, A. M., et al. (2011). "Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease." Molecular Pharmacology **79**(6): 964-973.

Microglial activation is an invariant feature of Alzheimer's disease (AD). It is noteworthy that cannabinoids are neuroprotective by preventing -amyloid (A)-induced microglial activation both in vitro and in vivo. On the other hand, the phytocannabinoid cannabidiol (CBD) has shown anti-inflammatory properties in different paradigms. In the present study, we compared the effects of CBD with those of other cannabinoids on microglial cell functions in vitro and on learning behavior and cytokine expression after A intraventricular administration to mice.

CBD, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo-[1,2,3-d,e]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone [WIN 55,212-2 (WIN)], a mixed CB(1)/CB(2) agonist, and 1,1-dimethylbutyl-1-deoxy-(9)-tetrahydrocannabinol [JWH-133 (JWH)], a CB(2)-selective agonist, concentration-dependently decreased ATP-induced (400 uM) increase in intracellular calcium ([Ca(2+)](i)) in cultured N13 microglial cells and in rat primary microglia. In contrast, 4-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methanol [HU-308 (HU)], another CB(2) agonist, was without effect. Cannabinoid and adenosine A(2A) receptors may be involved in the CBD action. CBD- and WIN-promoted primary microglia migration was blocked by CB(1) and/or CB(2) antagonists. JWH and HU-induced migration was blocked by a CB(2) antagonist only. All of the cannabinoids decreased lipopolysaccharide-induced nitrite generation, which was insensitive to cannabinoid antagonism. Finally, both CBD and WIN, after subchronic administration for 3 weeks, were able to prevent learning of a spatial navigation task and cytokine gene expression in -amyloid-injected mice. In summary, CBD is able to modulate microglial cell function in vitro and induce beneficial effects in an in vivo model of AD. Given that CBD lacks psychoactivity, it may represent a novel therapeutic approach for this neurological disease.

McDougall, J. J. (2011). "Peripheral analgesia: Hitting pain where it hurts." Biochimica et Biophysica Acta **1812**(4): 459-467.

Pain is a complex biological phenomenon that encompasses intricate neurophysiological, behavioural, psychosocial and affective components. Protracted or chronic pain alerts an individual to a possible pathological abnormality and is the main reason why patients visit a primary care physician. Despite the pervasiveness of chronic pain in the population, the effectiveness of current pharmacological therapies remains woefully inadequate and prolonged treatment often leads to the development of undesirable side-effects. Since the vast majority of chronic pain originates in a specific tissue or group of tissues, it may be advantageous to target pain control in the periphery and thereby circumvent the known risks associated with non-specific systemic treatments. This review spotlights a number of promising targets for peripheral pain control including the transient receptor potential (TRP) family of neuronal ion channels, the family of proteinase activated receptors (PARs), cannabinoids, and opioids. A critical appraisal of these targets in preclinical models of disease is given and their suitability as future peripheral analgesics is discussed. 

Meisel, K. and J. H. Friedman (2012). "Medical marijuana in Huntington's disease: report of two cases." Medicine & Health, Rhode Island **95**(6): 178-179.

Milburn, J. B. (2010). "Medical marijuana. A smoking-hot business opportunity?" Mgma Connexion/Medical Group Management Association **10**(9): 25-26.

Miller, J. B., et al. (2010). "Pediatric cannabinoid hyperemesis: two cases." Pediatric

Emergency Care **26**(12): 919-920.

Cannabinoid hyperemesis has recently been described in the literature. It is a syndrome characterized by severe nausea and hyperemesis in the setting of chronic marijuana abuse and, to date, has been described only in adults. We describe the syndrome in 2 pediatric patients, for whom extensive gastrointestinal workups failed to identify a clear cause and cessation of marijuana use resulted in the alleviation of their symptoms. As in most published adult cases, compulsive bathing was present in both of these cases.

Mulder, J., et al. (2011). "Molecular reorganization of endocannabinoid signalling in Alzheimer's disease." Brain **134**(Pt 4): 1041-1060.

Retrograde messengers adjust the precise timing of neurotransmitter release from the presynapse, thus modulating synaptic efficacy and neuronal activity. 2-Arachidonoyl glycerol, an endocannabinoid, is one such messenger produced in the postsynapse that inhibits neurotransmitter release upon activating presynaptic CB(1) cannabinoid receptors. Cognitive decline in Alzheimer's disease is due to synaptic failure in hippocampal neuronal networks. We hypothesized that errant retrograde 2-arachidonoyl glycerol signalling impairs synaptic neurotransmission in Alzheimer's disease. Comparative protein profiling and quantitative morphometry showed that overall CB(1) cannabinoid receptor protein levels in the hippocampi of patients with Alzheimer's disease remain unchanged relative to age-matched controls, and CB(1) cannabinoid receptor-positive presynapses engulf amyloid--containing senile plaques. Hippocampal protein concentrations for the sn-1-diacylglycerol lipase and isoforms, synthesizing 2-arachidonoyl glycerol, significantly increased in definite Alzheimer's (Braak stage VI), with ectopic sn-1-diacylglycerol lipase expression found in microglia accumulating near senile plaques and apposing CB(1) cannabinoid receptor-positive presynapses. We found that microglia, expressing two 2-arachidonoyl glycerol-degrading enzymes, serine hydrolase /-hydrolase domain-containing 6 and monoacylglycerol lipase, begin to surround senile plaques in probable Alzheimer's disease (Braak stage III). However, Alzheimer's pathology differentially impacts serine hydrolase /-hydrolase domain-containing 6 and monoacylglycerol lipase in hippocampal neurons: serine hydrolase /-hydrolase domain-containing 6 expression ceases in neurofibrillary tangle-bearing pyramidal cells. In contrast, pyramidal cells containing hyperphosphorylated tau retain monoacylglycerol lipase expression, although at levels significantly lower than in neurons lacking neurofibrillary pathology. Here, monoacylglycerol lipase accumulates in CB(1) cannabinoid receptor-positive presynapses. Subcellular fractionation revealed impaired monoacylglycerol lipase recruitment to biological membranes in post-mortem Alzheimer's tissues, suggesting that disease progression slows the termination of 2-arachidonoyl glycerol signalling. We have experimentally confirmed that altered 2-arachidonoyl glycerol signalling could contribute to synapse silencing in Alzheimer's disease by demonstrating significantly prolonged depolarization-induced suppression of inhibition when superfusing mouse hippocampi with amyloid-. We propose that the temporal dynamics and cellular specificity of molecular rearrangements impairing 2-

arachidonoyl glycerol availability and actions may differ from those of anandamide. Thus, enhanced endocannabinoid signalling, particularly around senile plaques, can exacerbate synaptic failure in Alzheimer's disease.

Muller-Vahl, K. R. (2009). "Tourette's syndrome." Current Topics in Behavioral Neurosciences **1**: 397-410.

Tourette's syndrome (TS) is a chronic disorder characterized by motor and vocal tics and a variety of associated behaviour disorders. Because current therapy is often unsatisfactory, there is expanding interest in new therapeutic strategies that are more effective, cause less side effects and ameliorate not only tics but also behavioural problems. From anecdotal reports and preliminary controlled studies it is suggested that - at least in a subgroup of patients - cannabinoids are effective in the treatment of TS. While most patients report beneficial effects when smoking marijuana (Cannabis sativa L.), available clinical trials have been performed using oral 9-tetrahydrocannabinol (THC). In otherwise treatment-resistant TS patients, therefore, therapy with THC should not be left unattempted. To date, it is unknown whether other drugs that interact with the endocannabinoid receptor system might be more effective in the treatment of TS than smoked marijuana or pure THC. Since it has been suggested that abnormalities within the endocannabinoid receptor system might underlie TS pathophysiology, it would be of interest to investigate the effect of substances that for example bind more selectively to the central cannabinoid receptor or inhibit the uptake or the degradation of different endocannabinoids.

Murineddu, G., et al. (2012). "A survey of recent patents on CB2 agonists in the management of pain." Recent Patents on CNS Drug Discovery **7**(1): 4-24.

Pain, a homeostatic and protective mechanism which can go awry in disease states and therefore needs treatment, is a complex and differentiated sensorial perception which may be classified as physiological, inflammatory and neuropathic. Chronic pain represents a major health problem throughout the world, thus several companies and researchers have embarked on the search for new drugs and targets to treat the disease. The different types of receptors in the CNS involved in the mediation of analgesia include the cannabinoid receptors: in particular, CB2 modulators seem to represent a new potential class of analgesic. This review covers recent patents and advances in CB2 agonist studies in the management of pain.

Nandi, P. R. (2012). "Pain in neurological conditions." Current Opinion in Supportive & Palliative Care **6**(2): 194-200.

PURPOSE OF REVIEW: To address the issues of the scale and diversity of chronic pain in neurological disorders and the evidence for effective treatment of pain in these conditions.

RECENT FINDINGS: Contemporary literature supports the notion that pain in neurological conditions is common and has tended to be underestimated.

SUMMARY: Pain in neurological disease displays great diversity in putative mechanisms and clinical presentation. Rational management requires an analysis

of likely mechanisms of pain generation as a guide to treatment. Some common neurological disorders are briefly discussed, primarily to provide an indication of the range of pain phenotypes observed across the spectrum of neurological disease. Treatments are reviewed with an emphasis on systemic drugs and the current best evidence for their use.

Nelson, R. (2011). "Cannabis use in long-term care: an emerging issue for nurses." American Journal of Nursing **111**(4): 19-20.

Nicolson, S. E., et al. (2012). "Cannabinoid hyperemesis syndrome: a case series and review of previous reports." Psychosomatics **53**(3): 212-219.

BACKGROUND: Cannabis is the most commonly used illicit substance worldwide. Cannabinoids or cannabinoid receptor agonists are often used to treat nausea, vomiting, and anorexia. However, in recent years, several medical journals have published reports of patients with nausea and vomiting thought to be induced by chronic cannabis use.

OBJECTIVE: The authors seek to inform readers about Cannabinoid Hyperemesis Syndrome (CHS).

METHOD: The authors describe four patients with chronic cannabis abuse, episodic, intractable nausea and vomiting, and compulsive hot water bathing. Previous cases of CHS are reviewed, pathophysiology is hypothesized, and difficulties with making the diagnosis are discussed.

CONCLUSION: CHS should be strongly considered in the differential diagnosis of patients with intractable vomiting and/or compulsive hot water bathing. Copyright 2012 The Academy of Psychosomatic Medicine. Published by Elsevier Inc. All rights reserved.

Notcutt, W., et al. (2012). "A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex (nabiximols)." Multiple Sclerosis **18**(2): 219-228.

BACKGROUND: Open-label studies are not ideal for providing robust evidence for long-term maintenance of efficacy of medicines, especially where medicines provide symptom relief and where long-term use of a placebo may be problematic and not ethical.

OBJECTIVE: To evaluate the maintenance of efficacy of Sativex in subjects who have gained long-term symptomatic relief of spasticity in multiple sclerosis (MS), and to assess the impact of sudden medicine withdrawal.

METHODS: An enriched enrolment randomized withdrawal study design was used. Eligible subjects with ongoing benefit from Sativex for at least 12 weeks entered this 5-week placebo-controlled, parallel-group, randomized withdrawal study. Each subjects' previous effective and tolerated dose was continued.

RESULTS: A total of 18 subjects per group were enrolled. Demographics showed a mean duration of MS of 16.4 years, spasticity 12.7 years, mean duration of Sativex use of 3.6 years (median 3.4 years) and a mean daily dose of 8.25 sprays. Primary outcome of time to treatment failure was significantly in favour of Sativex ($p = 0.013$). Secondary endpoints showed significant changes in the Carer and

Subject's Global Impression of Change scales in favour of Sativex.
CONCLUSIONS: Maintenance of Sativex efficacy in long-term symptomatic improvement of spasticity to a group of subjects with MS has been confirmed using this study design.

Nussbaum, A., et al. (2011). "Medical marijuana use and suicide attempt in a patient with major depressive disorder." American Journal of Psychiatry **168**(8): 778-781.

Oreja-Guevara, C. (2012). "Clinical efficacy and effectiveness of Sativex, a combined cannabinoid medicine, in multiple sclerosis-related spasticity." Expert Review of Neurotherapeutics **12**(4 Suppl): 3-8.

Multiple sclerosis (MS) is associated with a wide range of disease symptoms and amongst these, spasticity is one of the most disabling and has the greatest impact on patient well-being and quality of life. Until now, available drug therapies for spasticity appear to have limited benefit and are often associated with poor tolerability. In a recent Spanish survey it was noted that multidrug therapy and a low control rate were common features for a large proportion of patients with MS-related spasticity, suggesting that currently available monotherapies lack significant activity. Sativex is a 1:1 mixture of -9-tetrahydrocannabinol and cannabidiol derived from Cannabis sativa chemovars, which is available as an oromucosal spray. Clinical experience with Sativex in patients with MS-related spasticity is steadily accumulating. Results from randomized, controlled trials have reported a reduction in the severity of symptoms associated with spasticity, leading to a better ability to perform daily activities and an improved perception of patients and their carers regarding functional status. These are highly encouraging findings that provide some much needed optimism for the treatment of this disabling and often painful symptom of MS.

Orellana, J. A., et al. (2012). "Glial hemichannels and their involvement in aging and neurodegenerative diseases." Reviews in the Neurosciences **23**(2): 163-177.

During the last two decades, it became increasingly evident that glial cells accomplish a more important role in brain function than previously thought. Glial cells express pannexins and connexins, which are member subunits of two protein families that form membrane channels termed hemichannels. These channels communicate intra- and extracellular compartments and allow the release of autocrine/paracrine signaling molecules [e.g., adenosine triphosphate (ATP), glutamate, nicotinamide adenine dinucleotide, and prostaglandin E2] to the extracellular milieu, as well as the uptake of small molecules (e.g., glucose). An increasing body of evidence has situated glial hemichannels as potential regulators of the beginning and maintenance of homeostatic imbalances observed in diverse brain diseases. Here, we review and discuss the current evidence about the possible role of glial hemichannels on neurodegenerative diseases. A subthreshold pathological threatening condition leads to microglial activation, which keeps active defense and restores the normal function of the central nervous system. However, if the stimulus is deleterious, microglial cells and the endothelium become overactivated, both releasing bioactive molecules (e.g.,

glutamate, cytokines, prostaglandins, and ATP), which increase the activity of glial hemichannels, reducing the astroglial neuroprotective functions, and further reducing neuronal viability. Because ATP and glutamate are released via glial hemichannels in neurodegenerative conditions, it is expected that they contribute to neurotoxicity. More importantly, toxic molecules released via glial hemichannels could increase the Ca2+ entry in neurons also via neuronal hemichannels, leading to neuronal death. Therefore, blockade of hemichannels expressed by glial cells and/or neurons during neuroinflammation might prevent neurodegeneration.

Pant, S., et al. (2012). "Spicy seizure." American Journal of the Medical Sciences **344**(1): 67-68.

Despite the widespread use of illegal synthetic cannabinoids, report of serious toxicity following its use of is rare. The authors report a case of severe toxicity after intentional inhalation of the synthetic cannabinoid JWH-018.

Parker, L. A., et al. (2011). "Regulation of nausea and vomiting by cannabinoids." British Journal of Pharmacology **163**(7): 1411-1422.

Considerable evidence demonstrates that manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge. CB(1) agonism suppresses vomiting, which is reversed by CB(1) antagonism, and CB(1) inverse agonism promotes vomiting. Recently, evidence from animal experiments suggests that cannabinoids may be especially useful in treating the more difficult to control symptoms of nausea and anticipatory nausea in chemotherapy patients, which are less well controlled by the currently available conventional pharmaceutical agents. Although rats and mice are incapable of vomiting, they display a distinctive conditioned gaping response when re-exposed to cues (flavours or contexts) paired with a nauseating treatment. Cannabinoid agonists ((9) -THC, HU-210) and the fatty acid amide hydrolase (FAAH) inhibitor, URB-597, suppress conditioned gaping reactions (nausea) in rats as they suppress vomiting in emetic species. Inverse agonists, but not neutral antagonists, of the CB(1) receptor promote nausea, and at subthreshold doses potentiate nausea produced by other toxins (LiCl). The primary non-psychoactive compound in cannabis, cannabidiol (CBD), also suppresses nausea and vomiting within a limited dose range. The anti-nausea/anti-emetic effects of CBD may be mediated by indirect activation of somatodendritic 5-HT(1A) receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions. Preclinical research indicates that cannabinioids, including CBD, may be effective clinically for treating both nausea and vomiting produced by chemotherapy or other therapeutic treatments. 2011 The Authors. British Journal of Pharmacology 2011 The British Pharmacological Society.

Pini, A., et al. (2012). "The role of cannabinoids in inflammatory modulation of allergic respiratory disorders, inflammatory pain and ischemic stroke." Current Drug Targets

**13**(7): 984-993.

This review is intended to offer updated information on the involvement of cannabinoids in the process of inflammation, focusing on immune/allergic reactions, inflammatory pain and neuroinflammation and discussing the interactions among endocannabinoid metabolism, prostanoids and nitric oxide. Two types of cannabinoid receptors, CB1 and CB2, which belong to the G protein-coupled receptor family, have been identified and are targeted by numerous exogenous and endogenous ligands. The activation of CB2 receptors on mast cells has direct antiinflammatory effects, causing decreased release of pro-inflammatory mediators by these cells. The activation of CB1 receptors on bronchial nerve endings has bronchodilator effects by acting on the airway smooth muscle and may be beneficial in airway hyperreactivity and asthma. Moreover, pharmacologic interference with endocannabinoid metabolism has been demonstrated to result in anti-nociceptive activity, mediated by CB1 and CB2 receptors, in animal models of inflammatory pain. The presence of endocannabinoid machinery in the central nervous system, together with high levels of CB1 expression, suggests that the endocannabinoid system is an important modulator of neuroinflammation and a possible drug target. In selected conditions, the activation of CB1 receptors in cerebral blood vessels can have beneficial antiischemic effects. However, as endocannabinoids can also bind to vanilloid receptors, they may also mediate neurotoxic effects.

Pisani, V., et al. (2011). "Homeostatic changes of the endocannabinoid system in Parkinson's disease." Movement Disorders **26**(2): 216-222.

Endocannabinoids (eCBs) are endogenous lipids that bind principally type-1 and type-2 cannabinoid (CB(1) and CB(2)) receptors. N-Arachidonoylethanolamine (AEA, anandamide) and 2-arachidonoylglycerol (2-AG) are the best characterized eCBs that are released from membrane phospholipid precursors through multiple biosynthetic pathways. Together with their receptors and metabolic enzymes, eCBs form the so-called "eCB system". The later has been involved in a wide variety of actions, including modulation of basal ganglia function. Consistently, both eCB levels and CB(1) receptor expression are high in several basal ganglia regions, and more specifically in the striatum and in its target projection areas. In these regions, the eCB system establishes a close functional interaction with dopaminergic neurotransmission, supporting a relevant role for eCBs in the control of voluntary movements. Accordingly, compelling experimental and clinical evidence suggests that a profound rearrangement of the eCB system in the basal ganglia follows dopamine depletion, as it occurs in Parkinson's disease (PD). In this article, we provide a brief survey of the evidence that the eCB system changes in both animal models of, and patients suffering from, PD. A striking convergence of findings is observed between both rodent and primate models and PD patients, indicating that the eCB system undergoes dynamic, adaptive changes, aimed at restoring an apparent homeostasis within the basal ganglia network. Copyright 2010 Movement Disorder Society.

Portenoy, R. K., et al. (2012). "Nabiximols for opioid-treated cancer patients with poorly-

controlled chronic pain: a randomized, placebo-controlled, graded-dose trial." Journal of Pain **13**(5): 438-449.

Patients with advanced cancer who have pain that responds poorly to opioid therapy pose a clinical challenge. Nabiximols (Nabiximols is the U.S. Adopted Name [USAN] for Sativex [GW Pharma Ltd, Wiltshire, U.K.], which does not yet have an INN), a novel cannabinoid formulation, is undergoing investigation as add-on therapy for this population. In a randomized, double-blind, placebo-controlled, graded-dose study, patients with advanced cancer and opioid-refractory pain received placebo or nabiximols at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day). Average pain, worst pain and sleep disruption were measured daily during 5 weeks of treatment; other questionnaires measured quality of life and mood. A total of 360 patients were randomized; 263 completed. There were no baseline differences across groups. The 30% responder rate primary analysis was not significant for nabiximols versus placebo (overall P = .59). A secondary continuous responder analysis of average daily pain from baseline to end of study demonstrated that the proportion of patients reporting analgesia was greater for nabiximols than placebo overall (P = .035), and specifically in the low-dose (P = .008) and medium-dose (P = .039) groups. In the low-dose group, results were similar for mean average pain (P = .006), mean worst pain (P = .011), and mean sleep disruption (P = .003). Other questionnaires showed no significant group differences. Adverse events were dose-related and only the high-dose group compared unfavorably with placebo. This study supports the efficacy and safety of nabiximols at the 2 lower-dose levels and provides important dose information for future trials. PERSPECTIVE: Nabiximols, a novel cannabinoid formulation, may be a useful add-on analgesic for patients with opioid-refractory cancer pain. A randomized, double-blind, placebo-controlled, graded-dose study demonstrated efficacy and safety at low and medium doses. Copyright 2012 American Pain Society. Published by Elsevier Inc. All rights reserved.

Price, S. L., et al. (2011). "Cannabinoid hyperemesis syndrome as the underlying cause of intractable nausea and vomiting." Journal of the American Osteopathic Association **111**(3): 166-169.

Recently, reports have suggested that chronic cannabis abuse can result in cyclical vomiting, or cannabinoid hyperemesis syndrome. With the increasing prevalence of cannabis use in the United States, this syndrome may be encountered in the emergency department. The authors describe a case of a 30-year-old man who presented to the emergency department with diffuse abdominal pain, nausea, and intractable vomiting. He reported symptomatic relief with prolonged hot showers. Results of a urine drug screen were positive for cannabis, and the patient admitted to chronic cannabis use for years. Results of the drug screen, combined with the patient's symptomatic relief with hot showers, led to the diagnosis of cannabinoid hyperemesis syndrome. The patient was admitted to the hospital and underwent pharmaceutical treatment. However, hot showers continued to be the mainstay of the patient's symptomatic relief. Four days after presentation, the patient's symptoms resolved and he was discharged from the hospital.

Pryce, G. and D. Baker (2012). "Potential control of multiple sclerosis by cannabis and the endocannabinoid system." CNS & Neurological Disorders Drug Targets **11**(5): 624-641.

> For many years, multiple sclerosis (MS) patients have been self-medicating with illegal street cannabis to alleviate symptoms associated with MS. Data from animal models of MS and clinical studies have supported the anecdotal data that cannabis can improve symptoms such as limb spasticity, which are commonly associated with progressive MS, by the modulation of excessive neuronal signalling. This has lead to cannabis-based medicines being approved for the treatment of pain and spasticity in MS for the first time. Experimental studies into the biology of the endocannabinoid system have revealed that cannabinoids have activity, not only in symptom relief but also potentially in neuroprotective strategies which may slow disease progression and thus delay the onset of symptoms such as spasticity. This review appraises the current knowledge of cannabinoid biology particularly as it pertains to MS and outlines potential future therapeutic strategies for the treatment of disease progression in MS.

Qi, J., et al. (2011). "Painful pathways induced by TLR stimulation of dorsal root ganglion neurons." Journal of Immunology **186**(11): 6417-6426.

> We hypothesize that innate immune signals from infectious organisms and/or injured tissues may activate peripheral neuronal pain signals. In this study, we demonstrated that TLRs 3, 7, and 9 are expressed by human dorsal root ganglion neurons (DRGNs) and in cultures of primary mouse DRGNs. Stimulation of murine DRGNs with TLR ligands induced expression and production of proinflammatory chemokines and cytokines CCL5 (RANTES), CXCL10 (IP-10), IL-1, IL-1, and PGE(2), which have previously been shown to augment pain. Further, TLR ligands upregulated the expression of a nociceptive receptor, transient receptor potential vanilloid type 1 (TRPV1), and enhanced calcium flux by TRPV1-expressing DRGNs. Using a tumor-induced temperature sensitivity model, we showed that in vivo administration of a TLR9 antagonist, known as a suppressive oligodeoxynucleotide, blocked tumor-induced temperature sensitivity. Taken together, these data indicate that stimulation of peripheral neurons by TLR ligands can induce nerve pain.

Rahn, E. J., et al. (2011). "Pharmacological characterization of AM1710, a putative cannabinoid CB2 agonist from the cannabilactone class: antinociception without central nervous system side-effects." Pharmacology, Biochemistry & Behavior **98**(4): 493-502.

> Cannabinoid CB(2) agonists produce antinociception without central nervous system (CNS) side-effects. This study was designed to characterize the pharmacological and antinociceptive profile of AM1710, a CB(2) agonist from the cannabilactone class of cannabinoids. AM1710 did not exhibit off-target activity at 63 sites evaluated. AM1710 also exhibited limited blood brain barrier penetration. AM1710 was evaluated in tests of antinociception and CNS activity. CNS side-effects were evaluated in a modified tetrad (tail flick, rectal temperature, locomotor activity and rota-rod). Pharmacological specificity was

established using CB(1) (SR141716) and CB(2) (SR144528) antagonists. AM1710 (0.1-10mg/kg i.p.) produced antinociception to thermal but not mechanical stimulation of the hindpaw. AM1710 (5mg/kg i.p.) produced a longer duration of antinociceptive action than the aminoalkylindole CB(2) agonist (R,S)-AM1241 (1mg/kg i.p.) at maximally antinociceptive doses. Antinociception produced by the low (0.1mg/kg i.p.) dose of AM1710 was blocked selectively by the CB(2) antagonist SR144528 (6mg/kg i.p.), whereas antinociception produced by the high dose of AM1710 (5mg/kg i.p.) was blocked by either SR144528 (6mg/kg i.p.) or SR141716 (6mg/kg i.p.). AM1710 did not produce hypoactivity, hypothermia, tail flick antinociception, or motor ataxia when evaluated in the tetrad at any dose. In conclusion, AM1710, a CB(2)-preferring cannabilactone, produced antinociception in the absence of CNS side-effects. Thus, any CB(1)-mediated antinociceptive effects of this compound may be attributable to peripheral CB(1) activity. The observed pattern of pharmacological specificity produced by AM1710 is consistent with limited blood brain barrier penetration of this compound and absence of CNS side-effects. Copyright 2011 Elsevier Inc. All rights reserved.

Reed, J. B. (2010). "Drugs and alcohol: palliation of a ubiquitous reality." West Virginia Medical Journal **106**(4 Spec No): 86.

Reisfield, G. M. (2010). "Medical cannabis and chronic opioid therapy." Journal of Pain & Palliative Care Pharmacotherapy **24**(4): 356-361.

Fourteen states and the District of Columbia have legalized the use of cannabis for medical purposes. A small, high-quality literature supports the efficacy of medical cannabis for the treatment of neuropathic pain. The smoked botanical product, however, is associated with a number of adverse medical and psychiatric consequences. Furthermore, experimental data indicate that acute use of cannabis results in impairment of every important metric related to the safe operation of a motor vehicle. Epidemiological data show associations between recent cannabis use and both psychomotor impairment and motor vehicle crashes, associations that are strengthened by the concomitant use of alcohol and other central nervous system depressants. Finally, data from pain clinics reveals an unusually high prevalence of cannabis use in nearly all age groups and an association between cannabis use and opioid and other substance misuse. Based on available data and expert opinion, concomitant use of cannabis and opioids is an absolute contraindication to the operation of a motor vehicle. In patients who use cannabis and are prescribed opioids, heightened vigilance for opioid- and other substance-related problems is warranted. It is appropriate to refrain from prescribing opioids to individuals using medical cannabis if there is reasonable suspicion that the combination will pose a risk to the patient or others.

Richards, B. L., et al. (2012). "Neuromodulators for pain management in rheumatoid arthritis." Cochrane Database of Systematic Reviews **1**: CD008921.

BACKGROUND: Pain management is a high priority for patients with rheumatoid arthritis (RA). Despite deficiencies in research data, neuromodulators

have gained widespread clinical acceptance as adjuvants in the management of patients with chronic musculoskeletal pain.

OBJECTIVES: The aim of this review was to determine the efficacy and safety of neuromodulators in pain management in patients with RA. Neuromodulators included in this review were anticonvulsants (gabapentin, pregabalin, phenytoin, sodium valproate, lamotrigine, carbamazepine, levetiracetam, oxcarbazepine, tiagabine and topiramate), ketamine, bupropion, methylphenidate, nefopam, capsaicin and the cannabinoids.

SEARCH METHODS: We performed a computer-assisted search of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, 4th quarter), MEDLINE (1950 to week 1 November 2010), EMBASE (Week 44, 2010) and PsycINFO (1806 to week 2 November 2010). We also searched the 2008 and 2009 American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) conference abstracts and performed a handsearch of reference lists of articles.

SELECTION CRITERIA: We included randomised controlled trials which compared any neuromodulator to another therapy (active or placebo, including non-pharmacological therapies) in adult patients with RA that had at least one clinically relevant outcome measure.

DATA COLLECTION AND ANALYSIS: Two blinded review authors independently extracted data and assessed the risk of bias in the trials. Meta-analyses were used to examine the efficacy of a neuromodulator on pain, depression and function as well as their safety.

MAIN RESULTS: Four trials with high risk of bias were included in this review. Two trials evaluated oral nefopam (52 participants) and one trial each evaluated topical capsaicin (31 participants) and oromucosal cannabis (58 participants).The pooled analyses identified a significant reduction in pain levels favouring nefopam over placebo (weighted mean difference (WMD) -21.16, 95% CI -35.61 to -6.71; number needed to treat (NNT) 2, 95% CI 1.4 to 9.5) after two weeks. There were insufficient data to assess withdrawals due to adverse events. Nefopam was associated with significantly more adverse events (RR 4.11, 95% CI 1.58 to 10.69; NNTH 9, 95% CI 2 to 367), which were predominantly nausea and sweating.In a mixed population trial, qualitative analysis of patients with RA showed a significantly greater reduction in pain favouring topical capsaicin over placebo at one and two weeks (MD -23.80, 95% CI -44.81 to -2.79; NNT 3, 95% CI 2 to 47; MD -34.40, 95% CI -54.66 to -14.14; NNT 2, 95% CI 1.4 to 6 respectively). No separate safety data were available for patients with RA, however 44% of patients developed burning at the site of application and 2% withdrew because of this.One small, low quality trial assessed oromucosal cannabis against placebo and found a small, significant difference favouring cannabis in the verbal rating score 'pain at present' (MD -0.72, 95% CI -1.31 to -0.13) after five weeks. Patients receiving cannabis were significantly more likely to suffer an adverse event (risk ratio (RR) 1.82, 95% CI 1.10 to 3.00; NNTH 3, 95% CI 3 to 13). These were most commonly dizziness (26%), dry mouth (13%) and light headedness (10%).

AUTHORS' CONCLUSIONS: There is currently weak evidence that oral nefopam,

topical capsaicin and oromucosal cannabis are all superior to placebo in reducing pain in patients with RA. However, each agent is associated with a significant side effect profile. The confidence in our estimates is not strong given the difficulties with blinding, the small numbers of participants evaluated and the lack of adverse event data. In some patients, however, even a small degree of pain relief may be considered worthwhile. Until further research is available, given the relatively mild nature of the adverse events, capsaicin could be considered as an add-on therapy for patients with persistent local pain and inadequate response or intolerance to other treatments. Oral nefopam and oromucosal cannabis have more significant side effect profiles however and the potential harms seem to outweigh any modest benefit achieved.

Riggs, P. K., et al. (2012). "A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men." Brain Research **1431**: 46-52.

RATIONALE: The endocannabinoid system is under active investigation as a pharmacological target for obesity management due to its role in appetite regulation and metabolism. Exogenous cannabinoids such as tetrahydrocannabinol (THC) stimulate appetite and food intake. However, there are no controlled observations directly linking THC to changes of most of the appetite hormones.

OBJECTIVES: We took the opportunity afforded by a placebo-controlled trial of smoked medicinal cannabis for HIV-associated neuropathic pain to evaluate the effects of THC on the appetite hormones ghrelin, leptin and PYY, as well as on insulin.

METHODS: In this double-blind cross-over study, each subject was exposed to both active cannabis (THC) and placebo.

RESULTS: Compared to placebo, cannabis administration was associated with significant increases in plasma levels of ghrelin and leptin, and decreases in PYY, but did not significantly influence insulin levels.

CONCLUSION: These findings are consistent with modulation of appetite hormones mediated through endogenous cannabinoid receptors, independent of glucose metabolism. 

Ritter, J. M. (2012). "Exploiting modern cannabinoid pharmacology for therapeutic gain?" British Journal of Clinical Pharmacology **73**(5): 671-673.

Robson, P. (2011). "Abuse potential and psychoactive effects of -9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine." Expert Opinion on Drug Safety **10**(5): 675-685.

INTRODUCTION: There is a growing consensus that cannabis dependence is a substantial and underappreciated problem. The key component responsible for the euphoric effects of cannabis and its dependence potential is -9-tetrahydrocannabinol (THC). THC-containing cannabinoid medicines theoretically pose a risk of abuse and dependence. AREAS COVERED: In order to evaluate the potential of Sativex to cause cannabis-like psychoactivity, abuse or dependence relevant data from all published papers have been reviewed along with the integrated safety analysis for Sativex use in multiple sclerosis (MS)

patients on file at GW Pharmaceuticals. EXPERT OPINION: In clinical trials, intoxication scores have been low and euphoria reported by only 2.2% of patients. Tolerance has not occurred, abrupt withdrawal has not resulted in a formal withdrawal syndrome, and no cases of abuse or diversion have been reported to date. A formal abuse liability study of Sativex in experienced cannabis smokers showed some abuse potential in comparison with placebo at higher doses, but scores were consistently lower than equivalent doses of THC. Evidence to date suggests that abuse or dependence on Sativex is likely to occur in only a very small proportion of recipients.

Safaa, A. M., et al. (2012). "Marijuana-induced recurrent acute coronary syndrome with normal coronary angiograms." Drug & Alcohol Review **31**(1): 91-94.

We report a case of a man in his 40s presented to the emergency department twice, 1 month apart, with severe ischaemic sounding chest pain within 1 h of smoking marijuana on both occasions. He had elevated serial biomarkers and ischaemic electrocardiogram changes. His coronary angiograms on both episodes were entirely normal along with normal echocardiogram. This potentially suggests a coronary vasospasm as an underlying mechanism for these non-ST elevation myocardial infarctions. This should alert clinicians and the public alike to this potential risk of cannabis use. 2011 Australasian Professional Society on Alcohol and other Drugs.

Sagar, D. R., et al. (2009). "Targeting the cannabinoid system to produce analgesia." Current Topics in Behavioral Neurosciences **1**: 275-287.

Cannabinoid receptors are present at key sites involved in the relay and modulation of nociceptive responses. The analgesic effects of the cannabinoid CB1 receptor are well described. The widespread distribution of these receptors in the brain does, however, also explain the side-effects associated with CB1 receptor agonists. The cannabinoid CB2 receptor also produces analgesic effects in models of acute, inflammatory and neuropathic pain. The sites and mechanisms of CB2 receptor-mediated analgesia are described herein. In addition to targeting cannabinoid receptors directly, protection of endocannabinoids (eCBs) from metabolism also produces analgesic effects. Indeed, reports that noxious stimulation elevates levels of eCBs in the spinal cord and brain provide further rationale for this approach. The effects of inhibition of fatty acid amide hydrolase (FAAH) on nociceptive responses in models of inflammatory and neuropathic pain are discussed.

Saghafi, N., et al. (2011). "Cannabinoids attenuate cancer pain and proliferation in a mouse model." Neuroscience Letters **488**(3): 247-251.

We investigated the effects of cannabinoid receptor agonists on (1) oral cancer cell viability in vitro and (2) oral cancer pain and tumor growth in a mouse cancer model. We utilized immunohistochemistry and Western blot to show that human oral cancer cells express CBr1 and CBr2. When treated with WIN55,212-2 (non-selective), ACEA (CBr1-selective) or AM1241 (CBr2-selective) agonists in vitro, oral cancer cell proliferation was significantly attenuated in a dose-dependent

manner. In vivo, systemic administration (0.013M) of WIN55,212-2, ACEA, or AM1241 significantly attenuated cancer-induced mechanical allodynia. Tumor growth was also significantly attenuated with systemic AM1241 administration. Our findings suggest a direct role for cannabinoid mechanisms in oral cancer pain and proliferation. The systemic administration of cannabinoid receptor agonists may have important therapeutic implications wherein cannabinoid receptor agonists may reduce morbidity and mortality of oral cancer. Copyright A 2010 Elsevier Ireland Ltd. All rights reserved.

Sagredo, O., et al. (2012). "Cannabinoids: novel medicines for the treatment of Huntington's disease." Recent Patents on CNS Drug Discovery **7**(1): 41-48.

Cannabinoid pharmacology has experienced a notable increase in the last 3 decades which is allowing the development of novel cannabinoid-based medicines for the treatment of different human pathologies, for example, Cesamet (nabilone) or Marinol (synthetic 9-tetrahydrocannabinol for oral administration) that were approved in 80s for the treatment of nausea and vomiting associated with chemotherapy treatment in cancer patients and in 90s for anorexiacachexia associated with AIDS therapy. Recently, the british company GW Pharmaceuticals plc has developed an oromucosal spray called Sativex, which is constituted by an equimolecular combination of 9-tetrahydrocannabinol- and cannabidiol- enriched botanical extracts. Sativex has been approved for the treatment of specific symptoms (i.e. spasticity and pain) of multiple sclerosis patients in various countries (i.e. Canada, UK, Spain, New Zealand). However, this cannabis- based medicine has been also proposed to be useful in other neurological disorders given the analgesic, antitumoral, anti-inflammatory, and neuroprotective properties of their components demonstrated in preclinical models. Numerous clinical trials are presently being conducted to confirm this potential in patients. We are particularly interested in the case of Huntington's disease (HD), an autosomal-dominant inherited disorder caused by an excess of CAG repeats in the genomic allele resulting in a polyQ expansion in the encoded protein called huntingtin, and that affects primarily striatal and cortical neurons thus producing motor abnormalities (i.e. chorea) and dementia. Cannabinoids have been studied for alleviation of hyperkinetic symptoms, given their inhibitory effects on movement, and, in particular, as disease-modifying agents due to their anti-inflammatory, neuroprotective and neuroregenerative properties. This potential has been corroborated in different experimental models of HD and using different types of cannabinoid agonists, including the phytocannabinoids present in Sativex, and we are close to initiate a clinical trial with this cannabis-based medicine to evaluate its capability as a disease-modifying agent in a population of HD patients. The present review will address all preclinical evidence supporting the potential of Sativex for the treatment of disease progression in HD patients. The article presents some promising patents on the cannabinoids.

Sanchez, A. J. and A. Garcia-Merino (2012). "Neuroprotective agents: cannabinoids." Clinical Immunology **142**(1): 57-67.

Chronic inflammation and neurodegeneration are the main pathological traits of

multiple sclerosis that coexist in all stages of the disease course, with complex and still nonclarified relationships. Currently licensed medications have efficacy to control aspects related to inflammation, but have been unable to modify pure progression. Experimental work has provided robust evidence of the immunomodulatory and neuroprotective properties that cannabinoids exert in animal models of multiple sclerosis. Through activation of the CB2 receptor, cannabinoids modulate peripheral blood lymphocytes, interfere with migration across the blood-brain barrier and control microglial/macrophage activation. CB1 receptors present in neural cells have a fundamental role in direct neuroprotection against several insults, mainly excitotoxicity. In multiple sclerosis, several reports have documented the disturbance of the endocannabinoid system. Considering the actions demonstrated experimentally, cannabinoids might be promising agents to target the main aspects of the human disease. 

Schmid, S. M., et al. (2011). "Cannabinoid hyperemesis syndrome: an underreported entity causing nausea and vomiting of pregnancy." Archives of Gynecology & Obstetrics **284**(5): 1095-1097.

INTRODUCTION: In the western world, cannabis is the most widely used drug of abuse. Cannabinoid hyperemesis syndrome, which seems to be a rare paradoxical reaction in individuals with a particular predisposition, is characterized by cyclic severe nausea and vomiting in long-term cannabis users. While the symptoms are unresponsive to antiemetic drugs, compulsive hot baths result in a considerable symptom relief.

METHODS: We report the first case of cannabinoid hyperemesis syndrome in pregnancy. A 26-year-old patient was admitted to our clinic in the 10th week of gestation.

CONCLUSION: Before undertaking time-consuming and expensive medical examinations to rule out other medical reasons for therapy-resistant hyperemesis in pregnancy, obstetricians should determine whether compulsive bathing or showering provides symptomatic relief and ask specific questions regarding possible/suspected cannabis consumption.

Schneir, A. B. and T. Baumbacher (2012). "Convulsions associated with the use of a synthetic cannabinoid product." Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology **8**(1): 62-64.

INTRODUCTION: Clinical presentations following the use of various "spice" or synthetic cannabinoids have included agitation, anxiety, emesis, hallucinations, psychosis, tachycardia, and unresponsiveness. Convulsions were described in a one report although there was not laboratory confirmation for synthetic cannabinoids. In another published report laboratory confirmation for a synthetic cannabinoid was done in which the patient manifested activity that was interpreted as a possible convulsion.

CASE REPORT: We describe a patient who had two witnessed generalized convulsions soon after smoking a "spice" product that we later confirmed to have four different synthetic cannabinoids.

DISCUSSION: Convulsions have only rarely been associated with marijuana exposures. Recreational use of synthetic cannabinoids is a very recent phenomenon and there is a very limited, albeit burgeoning, literature detailing the associated complications including convulsions we have reported here. The absence of anticonvulsant phytocannabinoids in spice products could potentially be one of multiple unknown mechanisms contributing to convulsions.

Shekhar, C. (2011). "Mixed signals: cannabinoid system offers new therapeutic possibilities as well as challenges." Chemistry & Biology **18**(5): 553-554.

Simonetto, D. A., et al. (2012). "Cannabinoid hyperemesis: a case series of 98 patients." Mayo Clinic Proceedings **87**(2): 114-119.

OBJECTIVE: To promote wider recognition and further understanding of cannabinoid hyperemesis (CH).

PATIENTS AND METHODS: We constructed a case series, the largest to date, of patients diagnosed with CH at our institution. Inclusion criteria were determined by reviewing all PubMed indexed journals with case reports and case series on CH. The institution's electronic medical record was searched from January 1, 2005, through June 15, 2010. Patients were included if there was a history of recurrent vomiting with no other explanation for symptoms and if cannabis use preceded symptom onset. Of 1571 patients identified, 98 patients (6%) met inclusion criteria.

RESULTS: All 98 patients were younger than 50 years of age. Among the 37 patients in whom duration of cannabis use was available, most (25 [68%]) reported using cannabis for more than 2 years before symptom onset, and 71 of 75 patients (95%) in whom frequency of use was available used cannabis more than once weekly. Eighty-four patients (86%) reported abdominal pain. The effect of hot water bathing was documented in 57 patients (58%), and 52 (91%) of these patients reported relief of symptoms with hot showers or baths. Follow-up was available in only 10 patients (10%). Of those 10, 7 (70%) stopped using cannabis and 6 of these 7 (86%) noted complete resolution of their symptoms.

CONCLUSION: Cannabinoid hyperemesis should be considered in younger patients with long-term cannabis use and recurrent nausea, vomiting, and abdominal pain. On the basis of our findings in this large series of patients, we propose major and supportive criteria for the diagnosis of CH. 

Spadari, M., et al. (2011). "Cannabis body packing: two case reports." Clinical Toxicology: The Official Journal of the American Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists **49**(9): 862-864.

INTRODUCTION: Body packing is a well-known means of narcotic carriage across international borders. The most common drugs carried are cocaine and heroin.

CASE DESCRIPTIONS: We describe 2 cases of cannabis body packing which occurred the same year in the South of France, one with complications: a 45-year-old male went to emergency for abdominal pain. A plain abdominal x-ray revealed multiple

foreign bodies in the gastrointestinal tract. It was confirmed by abdominal CT. The laparatomy confirmed peritonitis secondary to colonic perforation, and 34 filled condoms packages were extracted. After calling poison centre, toxicological analysis was performed on one package. The resin wrapped in cellophane contained 15% tetrahydrocannabinol (THC). The patient was discharged on day 12.

DISCUSSION/CONCLUSION: Cannabis body packing is rarely reported, and the only known complications have a mechanic etiology. Plain abdominal x-ray is the best method for detection and it can be confirmed by abdominal CT and toxicological analysis. Cannabis is the most important illicit drug used in the word. Also cannabis body packing is probably underestimated. Health care practitioners should be aware of the possibility of body packing when someone coming back from abroad complains of abdominal pain.

Ste-Marie, P. A., et al. (2012). "Association of herbal cannabis use with negative psychosocial parameters in patients with fibromyalgia." Arthritis care & research **64**(8): 1202-1208.

OBJECTIVE: Patients with chronic pain, including fibromyalgia (FM), may seek treatments outside of mainstream medicine. Medicinal cannabinoids are popularly advocated for pain relief but with limited evidence for efficacy in FM. The extent of use of cannabinoids in FM is unknown.

METHODS: We have documented the self-reported prevalence of cannabinoid use in 457 patients with the diagnosis of FM and referred to a tertiary care pain center. We validated the diagnosis of FM and examined the associations of cannabinoid use in these patients.

RESULTS: Cannabinoids were being used by 13% of all patients, of whom 80% used herbal cannabis (marijuana), 24% used prescription cannabinoids, and 3% used both herbal cannabis and prescription cannabinoids. One-third of all men used cannabinoids. Current unstable mental illness (36% versus 23%; P = 0.002), opioid drug-seeking behavior (17% versus 4%; P = 0.002), and male sex (26% versus 7%; P = 0.0002) were all associated with herbal cannabis use. There was a trend for cannabinoid users to be unemployed and receiving disability payments. The diagnosis of FM was validated in 302 patients, with 155 assigned another primary diagnosis. When the FM group was analyzed separately, significant associations were lost, but trends remained.

CONCLUSION: Cannabinoids were used by 13% of patients referred with a diagnosis of FM. The association of herbal cannabis use with negative psychosocial parameters raises questions regarding the motive for this self-medication practice. Although cannabinoids may offer some therapeutic effect, caution regarding any recommendation should be exercised pending clarification of general health and psychosocial problems, especially for those self-medicating. Copyright 2012 by the American College of Rheumatology.

Szumita, R. P., et al. (2010). "Understanding and managing patients with chronic pain." Oral & Maxillofacial Surgery Clinics of North America **22**(4): 481-494.

The specialty of oral and maxillofacial surgery has had at its core the foundations

of anesthesia and pain and anxiety control. This article attempts to refamiliarize the reader with clinical pearls helpful in the management of patients with chronic pain conditions. The authors also hope to highlight the interplay of chronic pain and psychology as it relates to the oral and maxillofacial surgery patient. To that end, the article outlines and reviews the neurophysiology of pain, the definitions of pain, conditions encountered by the oral and maxillofacial surgeon that produce chronic pain, the psychological impact and comorbidities associated with patients experiencing chronic pain conditions, and concepts of multimodal treatment for patients experiencing chronic pain conditions. Copyright 2010 Elsevier Inc. All rights reserved.

Talwar, R. and V. K. Potluri (2011). "Cannabinoid 1 (CB1) receptor--pharmacology, role in pain and recent developments in emerging CB1 agonists." CNS & Neurological Disorders Drug Targets **10**(5): 536-544.

Cannabinoids are antinociceptive in animal models of acute pain, tissue injury and nerve injury induced nociception and act via their cognate receptors, cannabinoid receptor 1 and 2. This review examines the underlying biology of the endocannabinoids and behavioural, neurophysiological, neuroanatomical evidence supporting the notion of pain modulation by these ligands with a focus on the current evidence encompassing the pharmacological characterization of CB1 agonists in this therapy. Separating the psychotropic effects of CB1 agonists from their therapeutic benefits is the major challenge facing researchers in the field today and with the discovery of peripherally acting agonists there seems to be a ray of hope emerging for the diverse potential therapeutic applications of this class of ligands.

Thaler, A., et al. (2011). "Cannabinoids for pain management." Advances in Psychosomatic Medicine **30**: 125-138.

Cannabinoids have been used for thousands of years to provide relief from suffering, but only recently have they been critically evaluated in clinical trials. This review provides an in-depth examination of the evidence supporting cannabinoids in various pain states, along with an overview of potential adverse effects. In summary, there is strong evidence for a moderate analgesic effect in peripheral neuropathic and central pain conditions, and conflicting evidence for their use in nociceptive pain. For spasticity, most controlled studies demonstrate significant improvement. Adverse effects are not uncommon with cannabinoids, though most are not serious and self-limiting. In view of the limited effect size and low but not inconsequential risk of serious adverse events, cannabinoids should be employed as analgesics only when safer and more effective medication trials have failed, or as part of a multimodal treatment regimen. Copyright 2011 S. Karger AG, Basel.

Todaro, B. (2012). "Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting." Journal of the National Comprehensive Cancer Network **10**(4): 487-492.

Before the introduction of the serotonin receptor antagonists (5-HT3 receptor antagonists) in the early 1990s, limited effective options were available to prevent

and treat chemotherapy-induced nausea and vomiting (CINV). In 1985, the FDA approved 2 cannabinoid derivatives, dronabinol and nabilone, for the treatment of CINV not effectively treated by other agents. Today, the standard of care for prevention of CINV for highly and moderately emetogenic chemotherapy is a 5-HT3 receptor antagonist, dexamethasone, with or without aprepitant or fosaprepitant. With the approval of safer and more effective agents, cannabinoids are not recommended as first-line treatment for the prevention of CINV and are reserved for patients with breakthrough nausea and vomiting. Because of medical and legal concerns, the use of marijuana is not recommended for management of CINV and is not part of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis. Although patients may like to pursue this treatment option in states that have approved the use of marijuana for medical purposes, its use remains legally and therapeutically controversial.

Torres, S., et al. (2011). "A combined preclinical therapy of cannabinoids and temozolomide against glioma." Molecular Cancer Therapeutics **10**(1): 90-103.

Glioblastoma multiforme (GBM) is highly resistant to current anticancer treatments, which makes it crucial to find new therapeutic strategies aimed at improving the poor prognosis of patients suffering from this disease. (9)-Tetrahydrocannabinol (THC), the major active ingredient of marijuana, and other cannabinoid receptor agonists inhibit tumor growth in animal models of cancer, including glioma, an effect that relies, at least in part, on the stimulation of autophagy-mediated apoptosis in tumor cells. Here, we show that the combined administration of THC and temozolomide (TMZ; the benchmark agent for the management of GBM) exerts a strong antitumoral action in glioma xenografts, an effect that is also observed in tumors that are resistant to TMZ treatment. Combined administration of THC and TMZ enhanced autophagy, whereas pharmacologic or genetic inhibition of this process prevented TMZ + THC-induced cell death, supporting that activation of autophagy plays a crucial role on the mechanism of action of this drug combination. Administration of submaximal doses of THC and cannabidiol (CBD; another plant-derived cannabinoid that also induces glioma cell death through a mechanism of action different from that of THC) remarkably reduces the growth of glioma xenografts. Moreover, treatment with TMZ and submaximal doses of THC and CBD produced a strong antitumoral action in both TMZ-sensitive and TMZ-resistant tumors. Altogether, our findings support that the combined administration of TMZ and cannabinoids could be therapeutically exploited for the management of GBM. 2010 AACR.

Truini, A., et al. (2011). "Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy." CNS & Neurological Disorders Drug Targets **10**(8): 916-920.

We assessed the effect of palmitoylethanolamide (PEA) on pain and nerve function in patients with chemotherapy-induced painful neuropathy, in 20 patients undergoing thalidomide and bortezomib treatment for multiple myeloma. All patients were evaluated before and after a two-month treatment with PEA 300 mg BID using pain and warmth thresholds; blinded examiners measured motor and

sensory nerve fibre function and laser-evoked potentials. Although no variables returned to normal values, pain and all neurophysiological measures assessing A, A, and A fibres significantly improved ($P < 0.05$). In contrast, warmth thresholds, assessing unmyelinated afferents, remained unchanged ($P > 0.50$). Although a placebo effect might play a role in the reported pain relief, the changes in neurophysiological measures indicate that PEA exerted a positive action on myelinated fibre groups. PEA, possibly by moderating mast cell hyperactivity, relieved conduction blocks secondary to endoneural edema. In a severe condition such as painful neuropathy associated with multiple myeloma and chemotherapy, a safe substance such as PEA provides significant restoration of nerve function.

van Hasselt, J. G. C., et al. (2012). "Severe cannabinoid intoxication in a patient with non-small-cell lung cancer." Journal of Palliative Care **28**(1): 60-61.

Van Landeghem, A., et al. (2012). "Lung emphysema caused by marijuana smoking." Jbr-Btr: Organe de la Societe Royale Belge de Radiologie **95**(3): 166-167.

Wallace, E. A., et al. (2011). "Cannabinoid hyperemesis syndrome: literature review and proposed diagnosis and treatment algorithm." Southern Medical Journal **104**(9): 659-664.

Cannabinoid hyperemesis syndrome (CHS) is characterized by cyclic vomiting and compulsive bathing behaviors in chronic cannabis users. Patients are typically diagnosed with CHS only after multiple and extensive medical evaluations, consequently without a clear etiology of their symptoms or treatment plan leading to symptomatic improvement. Increased healthcare provider awareness of CHS as a cause of nausea, vomiting, and abdominal pain coupled with an attentiveness to focused history taking-especially noting symptomatic improvement with prolonged exposure to hot showers or baths-can lead to effective treatment through cannabis cessation. We propose a diagnosis and treatment algorithm for physicians to follow when evaluating patients presenting with nausea, vomiting, and abdominal pain who are suspected to suffer from CHS.

Walther, S., et al. (2011). "Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia." Journal of Clinical Psychopharmacology **31**(2): 256-258.

Ware, M. A. (2011). "Clearing the smoke around medical marijuana." Clinical Pharmacology & Therapeutics **90**(6): 769-771.

The hazy world of "medical marijuana" continues to cry out for clear data on which to base medical decision making and rational policy design. In this issue of Clinical Pharmacology & Therapeutics, Abrams and colleagues report that vaporized cannabis does not meaningfully affect opioid plasma levels and may even augment the efficacy of oxycodone and morphine in patients with chronic non-cancer pain. This Commentary considers the implications of this work for clinical practice and further research initiatives.

Wesnes, K. A., et al. (2010). "Nabilone produces marked impairments to cognitive

function and changes in subjective state in healthy volunteers." Journal of Psychopharmacology **24**(11): 1659-1669.

This was a double-blind, randomised, placebo-controlled, crossover study of the acute cognitive and subjective effects of nabilone 1-3 mg in healthy male volunteers. The Cognitive Drug Research computerised system (CDR system) was used to assess changes in attention, working and episodic memory. In addition, a number of self-ratings were conducted including those of mood, alertness and perceived drug effects. Impairments to attention, working and episodic memory and self-ratings of alertness were evident. Volunteers also experienced a number of subjective drug effects. These data demonstrate that acute doses of nabilone in the range 1-3 mg produce clear cognitive and subjective effects in healthy volunteers, and therefore they may be used as reference data in the future study of peripherally acting cannabinoids believed to be free from such effects.

Wild, K. and H. Wilson (2012). "Cannabinoid hyperemesis." Emergency Medicine Journal **29**(1): 67-69.

A 21-year-old woman presented with a 4-week history of sudden onset vomiting, nausea and anorexia. Questioning revealed that she had a 7-year history of heavy cannabis use (smoking). She did not describe abdominal pain, change in bowel habit, antibiotic use, foreign travel or contact with gastroenteritis. Biochemistry results demonstrated mild metabolic derangement with a low potassium and a low bicarbonate, and urine toxicology was positive for cannabinoids. Other investigations, including a full blood count, renal function tests, liver function tests, a coagulation sample, an ECG, urinary -hCG and a CT head scan, were all normal. A diagnosis of cannabinoid hyperemesis was made and her symptoms resolved after treatment with intravenous fluids, antiemetics and abstinence from cannabis. Since her discharge and abstinence she has had several relapses, each related to cannabis use and each resolving with abstinence. The patient is now seeking cognitive behavioural therapy to achieve permanent abstinence.

Wiley, J. L., et al. (2012). "3-Substituted pyrazole analogs of the cannabinoid type 1 (CB1) receptor antagonist rimonabant: cannabinoid agonist-like effects in mice via non-CB1, non-CB2 mechanism." Journal of Pharmacology & Experimental Therapeutics **340**(2): 433-444.

The prototypic cannabinoid type 1 (CB1) receptor antagonist/inverse agonist, rimonabant, is comprised of a pyrazole core surrounded by a carboxyamide with terminal piperidine group (3-substituent), a 2,4-dichlorophenyl group (1-substituent), a 4-chlorophenyl group (5-substituent), and a methyl group (4-substituent). Previous structure-activity relationship (SAR) analysis has suggested that the 3-position may be involved in receptor recognition and agonist activity. The goal of the present study was to develop CB1-selective compounds and explore further the SAR of 3-substitution on the rimonabant template. 3-Substituted analogs with benzyl and alkyl amino, dihydrooxazole, and oxazole moieties were synthesized and evaluated in vitro and in vivo. Several notable patterns emerged. First, most of the analogs exhibited CB1 selectivity, with many

lacking affinity for the CB2 receptor. Affinity tended to be better when [3H]5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (SR141716), rather than [3H](-)-cis-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-trans-4-(3-hydroxy-propyl)cyclohexanol (CP55,940), was used as the binding radioligand. Second, many of the analogs produced an agonist-like profile of effects in mice (i.e., suppression of activity, antinociception, hypothermia, and immobility); however, their potencies were not well correlated with their CB1 binding affinities. Further assessment of selected analogs showed that none were effective antagonists of the effects of 9-tetrahydrocannabinol in mice, their agonist-like effects were not blocked by rimonabant, they were active in vivo in CB1-/- mice, and they failed to stimulate guanosine-5'-O-(3-[35S]thio)-triphosphate binding. Several analogs were inverse agonists in the latter assay. Together, these results suggest that this series of 3-substituted pyrazole analogs represent a novel class of CB1-selective cannabinoids that produce agonist-like effects in mice through a non-CB1, non-CB2 mechanism.

Williams, B. (2011). "Legislatiye agenda 2011: focusing on priorities." Tennessee Medicine **104**(1): 29-32.

Xiong, W., et al. (2012). "Cannabinoids suppress inflammatory and neuropathic pain by targeting 3 glycine receptors." Journal of Experimental Medicine **209**(6): 1121-1134.

Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycinergic cannabinoids for chronic pain treatment. We report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the 3 GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified 3 GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the 3 GlyRs. Our findings suggest that the 3 GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.

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Young, A. C., et al. (2012). "Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation." American Journal of Emergency Medicine **30**(7): 1320.e1325-1327.

Synthetic cannabinoids have been popular recreational drugs of abuse for their psychoactive properties. Five of the many synthetic cannabinoids have been recently banned in the United States because of their unknown and potentially harmful adverse effects. Little is known about these substances. They are thought to have natural cannabinoid-like effects but have different chemical structures. Adverse effects related to synthetic cannabinoids are not well known. We provide clinical effects and patient outcome following K9 use. In addition, we briefly review synthetic cannabinoids. We present a 17-year-old adolescent boy with chest pain, tachycardia, and then bradycardia associated with smoking K9. Two synthetic cannabinoids, JWH-018 and JWH-073, were confirmed on laboratory analysis. In addition to the limited current data, we demonstrate harmful adverse effects related to toxicity of 2 synthetic cannabinoids. Further studies are needed. Published by Elsevier Inc.

Yu, X. H., et al. (2010). "A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain." Pain **151**(2): 337-344.

Cannabinoids are analgesic in man, but their use is limited by their psychoactive properties. One way to avoid cannabinoid receptor subtype 1 (CB1R)-mediated central side-effects is to develop CB1R agonists with limited CNS penetration. Activation of peripheral CB1Rs has been proposed to be analgesic, but the relative contribution of peripheral CB1Rs to the analgesic effects of systemic cannabinoids remains unclear. Here we addressed this by exploring the analgesic properties and site of action of AZ11713908, a peripherally restricted CB1R agonist, in rodent pain models. Systemic administration of AZ11713908 produced robust efficacy in rat pain models, comparable to that produced by WIN 55, 212-2, a CNS-penetrant, mixed CB1R and CB2R agonist, but AZ11713908 generated fewer CNS side-effects than WIN 55, 212-in a rat Irwin test. Since AZ11713908

is also a CB2R inverse agonist in rat and a partial CB2R agonist in mouse, we tested the specificity of the effects in CB1R and CB2R knock-out (KO) mice. Analgesic effects produced by AZ11713908 in wild-type mice with Freund's complete adjuvant-induced inflammation of the tail were completely absent in CB1R KO mice, but fully preserved in CB2R KO mice. An in vivo electrophysiological assay showed that the major site of action of AZ11713908 was peripheral. Similarly, intraplantar AZ11713908 was also sufficient to induce robust analgesia. These results demonstrate that systemic administration of AZ11713908, produced robust analgesia in rodent pain models via peripheral CB1R. Peripherally restricted CB1R agonists provide an interesting novel approach to analgesic therapy for chronic pain. 

Zajicek, J. P. and V. I. Apostu (2011). "Role of cannabinoids in multiple sclerosis." CNS Drugs **25**(3): 187-201.

Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS). The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged. Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established.

Zvolensky, M. J., et al. (2011). "Chronic pain and marijuana use among a nationally representative sample of adults." American Journal on Addictions **20**(6): 538-542.

This study sought to examine the relations between chronic pain and marijuana use in a large nationally representative survey of adults (n = 5,672; 53% female; M(age) = 45.05, SD = 17.9) conducted in the United States. After controlling for sociodemographic variables, lifetime history of depression, and alcohol abuse/dependence, there was a significant association between lifetime chronic

pain and lifetime and current marijuana use. Moreover, current chronic pain was significantly associated with lifetime marijuana use. There was no significant association between current chronic pain and current marijuana use, possibly owing to limited statistical power. Results suggest that there are generally consistent statistically significant relations between chronic pain and marijuana use. Future work is needed to explicate the developmental patterning between chronic pain and marijuana use. This paper presents the potential linkage between chronic pain and marijuana use. Results from this study suggest that it may be beneficial for clinicians to assess for marijuana use among patients suffering from chronic pain. Such patients may be using marijuana as a maladaptive coping strategy. 

***Updated Ovid MEDLINE***

Ovid MEDLINE(R) 1946 to November Week 2 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | Cannabis/ | 6724 | Advanced |
| 2 | cannabinoids/ | 5393 | Advanced |
| 3 | cannabidiol/ | 747 | Advanced |
| 4 | cannabinol/ | 193 | Advanced |
| 5 | Endocannabinoids/ | 4240 | Advanced |
| 6 | Marijuana Smoking/ | 2713 | Advanced |
| 7 | tetrahydrocannabinol/ | 5861 | Advanced |
| 8 | tetracannabinol*.mp. | 1 | Advanced |
| 9 | or/1-8 | 20489 | Advanced |
| 10 | exp Multiple Sclerosis/ | 44542 | Advanced |
| 11 | Muscle Spasticity/ | 6687 | Advanced |
| 12 | exp Migraine Disorders/ | 22020 | Advanced |
| 13 | Glioblastoma/ | 16306 | Advanced |
| 14 | exp Neurodegenerative Diseases/ | 218364 | Advanced |
| 15 | exp Epilepsy/ | 131214 | Advanced |
| 16 | exp Nausea/ | 16060 | Advanced |
| 17 | exp Pain/ | 309663 | Advanced |
| 18 | exp Movement Disorders/ | 106452 | Advanced |
| 19 | exp Parkinsonian Disorders/ | 58473 | Advanced |
| 20 | exp Dystonia/ | 7774 | Advanced |
| 21 | or/10-20 | 779554 | Advanced |
| 22 | 9 and 21 | 1745 | Advanced |
| 23 | exp animals/ not (exp animals/ and exp human/) | 4062536 | Advanced |
| 24 | 22 not 23 | 1209 | Advanced |
| 25 | limit 24 to english language | 1123 | Advanced |
| 26 | limit 25 to yr="2013 -Current" | 31 | Advanced |
| 27 | 2013*.em. | 738297 | Advanced |
| 28 | 25 and 27 | 75 | Advanced |

| | | | |
|---|---|---|---|
| 29 | 26 or 28 | 75 | Advanced |

Ovid MEDLINE(R) 1946 to November Week 2 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | Cannabis/ | 6724 | Advanced |
| 2 | cannabinoids/ | 5393 | Advanced |
| 3 | cannabidiol/ | 747 | Advanced |
| 4 | cannabinol/ | 193 | Advanced |
| 5 | Endocannabinoids/ | 4240 | Advanced |
| 6 | tetracannabinol*.mp. | 1 | Advanced |
| 7 | tetrahydrocannabinol/ | 5861 | Advanced |
| 8 | Marijuana Smoking/ | 2713 | Advanced |
| 9 | Marijuana Abuse/ | 4695 | Advanced |
| 10 | or/1-9 | 23937 | Advanced |
| 11 | exp Automobile Driving/ | 14401 | Advanced |
| 12 | exp Cognition Disorders/ | 63990 | Advanced |
| 13 | exp Psychomotor Disorders/ | 10886 | Advanced |
| 14 | Accidents, Traffic/ | 34797 | Advanced |
| 15 | Substance-Related Disorders/ | 80077 | Advanced |
| 16 | Substance Withdrawal Syndrome/ | 19679 | Advanced |
| 17 | Psychoses, Substance-Induced/ | 4540 | Advanced |
| 18 | Substance Abuse Detection/ | 6757 | Advanced |
| 19 | exp Depressive Disorder/ | 82588 | Advanced |
| 20 | Seizures/ | 41727 | Advanced |
| 21 | exp Nystagmus, Physiologic/ | 2783 | Advanced |
| 22 | Nystagmus, Pathologic/ | 7384 | Advanced |
| 23 | Postural Balance/ | 14668 | Advanced |
| 24 | exp Reaction Time/ | 86633 | Advanced |
| 25 | exp Psychomotor Performance/ | 89412 | Advanced |
| 26 | or/11-25 | 505729 | Advanced |
| 27 | 10 and 26 | 6509 | Advanced |
| 28 | exp animals/ not (exp animals/ and exp human/) | 4062536 | Advanced |
| 29 | 27 not 28 | 6048 | Advanced |

| | | | |
|---|---|---|---|
| 30 | limit 29 to english language | 5352 | Advanced |
| 31 | limit 30 to yr="2013 -Current" | 123 | Advanced |
| 32 | 2013*.em. | 738297 | Advanced |
| 33 | 30 and 32 | 258 | Advanced |
| 34 | 31 or 33 | 258 | Advanced |

***Ovid MEDLINE adverse effects***

Ovid MEDLINE(R) 1948 to February week 3 2011 # Searches Results Search Type
1 Cannabis/ae, po, to [Adverse Effects, Poisoning, Toxicity] 823 Advanced
2 exp Cannabinoids/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity] 978 Advanced
3 1 or 2 1714 Advanced
4 3 and automobile driving/ 46 Advanced
5 exp cognitive disorders/ or exp psychomotor disorders/ or accidents, traffice/ 9397 Advanced
6 exp cognition disorders/ or 5 54514 Advanced
7 3 and 6 78 Advanced
8 3 and ab.fs. 6 Advanced
9 exp Psychoses, Substance-Induced/ 6184 Advanced
10 exp Substance-Related Disorders/ or exp Substance Withdrawal Syndrome/ or exp Depressive Disorder/ 377983 Advanced
11 exp substance withdrawal syndrome/ or exp seizures/ci 29041 Advanced
12 3 and (9 or 11) 310 Advanced
13 Nystagmus, Physiologic/ or Nystagmus, Pathologic/ 7561 Advanced
14 3 and 13 1 Advanced
15 exp Postural Balance/ 10712 Advanced
16 Reaction Time/ 71342 Advanced
17 3 and (15 or 16) 45 Advanced
18 (*Cannabis/ae, po, to or exp *Cannabinoids/ae, ct, po, to) and acute*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 126 Advanced

19 4 or 7 or 8 or 12 or 14 or 17 or 18 521 Advanced
20 limit 19 to (english language and humans) 358 Advanced
21 (*Cannabis/ae, po, to or exp *Cannabinoids/ae, ct, po, to) and ci.fs. 315 Advanced
22 limit 21 to (english language and humans) 214 Advanced
23 20 or 22 465 Advanced
24 marijuana abuse/ae, co or marijuana smoking/ae, co 1143 Advanced
25 *marijuana abuse/ae, co or *marijuana smoking/ae, co 687 Advanced
26 limit 25 to (english language and humans) 578 Advanced
27 Substance Abuse Detection/ 5170 Advanced
28 exp Psychomotor Performance/ 69408 Advanced
29 (*Cannabis/ae, po, to or exp *Cannabinoids/ae, ct, po, to) and (27 or 28) 59 Advanced
30 limit 29 to (english language and humans) 52 Advanced
31 26 or 30 624

***Ovid MEDLINE updated January 22, 2013***

Ovid MEDLINE(R) 1946 to January Week 2 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | Cannabis/ | 6381 | Advanced |
| 2 | cannabinoids/ | 4671 | Advanced |
| 3 | cannabidiol/ | 615 | Advanced |
| 4 | cannabinol/ | 180 | Advanced |
| 5 | Endocannabinoids/ | 3276 | Advanced |
| 6 | Marijuana Smoking/ | 2184 | Advanced |
| 7 | tetrahydrocannabinol/ | 5344 | Advanced |
| 8 | or/1-7 | 17823 | Advanced |
| 9 | exp Multiple Sclerosis/ | 40315 | Advanced |
| 10 | Muscle Spasticity/ | 6269 | Advanced |
| 11 | exp Migraine Disorders/ | 20201 | Advanced |
| 12 | Glioblastoma/ | 13539 | Advanced |
| 13 | exp Neurodegenerative Diseases/ | 193108 | Advanced |
| 14 | exp Epilepsy/ | 120616 | Advanced |
| 15 | exp Nausea/ | 14693 | Advanced |
| 16 | exp Pain/ | 282471 | Advanced |
| 17 | exp Movement Disorders/ | 96455 | Advanced |
| 18 | exp Parkinsonian Disorders/ | 52196 | Advanced |
| 19 | exp Dystonia/ | 7276 | Advanced |
| 20 | or/9-19 | 705043 | Advanced |
| 21 | 8 and 20 | 1450 | Advanced |
| 22 | exp animals/ not (exp animals/ and exp human/) | 3747051 | Advanced |
| 23 | 21 not 22 | 1026 | Advanced |
| 24 | limit 23 to english language | 952 | Advanced |
| 25 | limit 24 to yr="2011 -Current" | 119 | Advanced |
| 26 | (2011* or 2012* or 2013*).em. | 1539146 | Advanced |
| 27 | 24 and 26 | 138 | Advanced |

| | | | |
|---|---|---|---|
| | | | Advanced |
| 28 | 25 or 27 | 138 | |

***Ovid MEDLINE updated January 28, 2013***

Ovid MEDLINE(R) 1946 to January Week 3 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | Cannabis/ | 6384 | Advanced |
| 2 | cannabinoids/ | 4675 | Advanced |
| 3 | cannabidiol/ | 617 | Advanced |
| 4 | cannabinol/ | 181 | Advanced |
| 5 | Endocannabinoids/ | 3285 | Advanced |
| 6 | tetracannabinol*.mp. | 1 | Advanced |
| 7 | tetrahydrocannabinol/ | 5348 | Advanced |
| 8 | Marijuana Smoking/ | 2189 | Advanced |
| 9 | Marijuana Abuse/ | 3877 | Advanced |
| 10 | or/1-9 | 20720 | Advanced |
| 11 | exp Automobile Driving/ | 13001 | Advanced |
| 12 | exp Cognition Disorders/ | 54031 | Advanced |
| 13 | exp Psychomotor Disorders/ | 10067 | Advanced |
| 14 | Accidents, Traffic/ | 32590 | Advanced |
| 15 | Substance-Related Disorders/ | 73108 | Advanced |
| 16 | Substance Withdrawal Syndrome/ | 18120 | Advanced |
| 17 | Psychoses, Substance-Induced/ | 4335 | Advanced |
| 18 | Substance Abuse Detection/ | 6064 | Advanced |
| 19 | exp Depressive Disorder/ | 74413 | Advanced |
| 20 | Seizures/ | 38831 | Advanced |
| 21 | exp Nystagmus, Physiologic/ | 2693 | Advanced |
| 22 | Nystagmus, Pathologic/ | 7184 | Advanced |
| 23 | Postural Balance/ | 12679 | Advanced |
| 24 | exp Reaction Time/ | 78237 | Advanced |
| 25 | exp Psychomotor Performance/ | 78939 | Advanced |
| 26 | or/11-25 | 455838 | Advanced |
| 27 | 10 and 26 | 5816 | Advanced |
| 28 | exp animals/ not (exp animals/ and exp human/) | 3749650 | Advanced |
| 29 | 27 not 28 | 5411 | Advanced |

| | | | |
|---|---|---|---|
| 30 | limit 29 to english language | 4748 | Advanced |
| 31 | limit 30 to yr="2011 -Current" | 373 | Advanced |
| 32 | (2011* or 2012* or 2013*).em. | 1555327 | Advanced |
| 33 | 30 and 32 | 458 | Advanced |

***PsycINFO updated January 24, 2013***

PsycINFO 1806 to January Week 3 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | cannabis/ | 2441 | Advanced |
| 2 | exp cannabinoids/ | 3175 | Advanced |
| 3 | marijuana/ | 1914 | Advanced |
| 4 | marijuana usage/ | 1792 | Advanced |
| 5 | cannabidiol*.mp. | 221 | Advanced |
| 6 | cannabinol*.mp. | 74 | Advanced |
| 7 | Endocannabinoid*.mp. | 1179 | Advanced |
| 8 | tetracannabinol*.mp. | 0 | Advanced |
| 9 | or/1-8 | 8690 | Advanced |
| 10 | multiple sclerosis/ | 6818 | Advanced |
| 11 | muscle spasms/ | 216 | Advanced |
| 12 | spasticity*.mp. | 1080 | Advanced |
| 13 | migraine headache/ | 6506 | Advanced |
| 14 | glioblastoma*.mp. | 515 | Advanced |
| 15 | exp neurodegenerative diseases/ | 43610 | Advanced |
| 16 | exp epilepsy/ | 17278 | Advanced |
| 17 | nausea/ | 592 | Advanced |
| 18 | exp pain/ | 37656 | Advanced |
| 19 | exp movement disorders/ | 19881 | Advanced |
| 20 | parkinsonism/ | 1984 | Advanced |
| 21 | dyston*.mp. | 2878 | Advanced |
| 22 | or/10-21 | 125296 | Advanced |
| 23 | 9 and 22 | 408 | Advanced |
| 24 | limit 23 to human | 203 | Advanced |
| 25 | limit 24 to english language | 194 | Advanced |
| 26 | limit 25 to yr="2011 -Current" | 34 | Advanced |
| 27 | (2011* or 2012* or 2013*).up. | 380778 | Advanced |
| 28 | 25 and 27 | 41 | Advanced |

| | | | |
|---|---|---|---|
| 29 | 26 or 28 | 41 | Advanced |

***PsycINFO updated November 26, 2013***

PsycINFO 1806 to November Week 3 2013

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | cannabis/ | 2697 | Advanced |
| 2 | exp cannabinoids/ | 3384 | Advanced |
| 3 | marijuana/ | 1999 | Advanced |
| 4 | marijuana usage/ | 1914 | Advanced |
| 5 | cannabidiol*.mp. | 247 | Advanced |
| 6 | cannabinol*.mp. | 78 | Advanced |
| 7 | Endocannabinoid*.mp. | 1314 | Advanced |
| 8 | tetracannabinol*.mp. | 0 | Advanced |
| 9 | or/1-8 | 9351 | Advanced |
| 10 | multiple sclerosis/ | 7612 | Advanced |
| 11 | muscle spasms/ | 232 | Advanced |
| 12 | spasticity*.mp. | 1210 | Advanced |
| 13 | migraine headache/ | 6901 | Advanced |
| 14 | glioblastoma*.mp. | 618 | Advanced |
| 15 | exp neurodegenerative diseases/ | 47713 | Advanced |
| 16 | exp epilepsy/ | 18624 | Advanced |
| 17 | nausea/ | 626 | Advanced |
| 18 | exp pain/ | 39805 | Advanced |
| 19 | exp movement disorders/ | 21470 | Advanced |
| 20 | parkinsonism/ | 2130 | Advanced |
| 21 | dyston*.mp. | 3146 | Advanced |
| 22 | or/10-21 | 135241 | Advanced |
| 23 | 9 and 22 | 454 | Advanced |
| 24 | limit 23 to human | 227 | Advanced |
| 25 | limit 24 to english language | 218 | Advanced |
| 26 | limit 25 to yr="2013 - Current" | 18 | Advanced |
| 27 | 2013*.up. | 172320 | Advanced |

| | | | |
|---|---|---|---|
| 28 | 25 and 27 | 23 | Advanced |
| 29 | 26 or 28 | 25 | Advanced |

***EMBASE updated January 23, 2013***

Embase 1974 to 2013 January 22

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | exp cannabinoid/ | 39905 | Advanced |
| 2 | cannabis/ | 21554 | Advanced |
| 3 | Cannabaceae/ | 42 | Advanced |
| 4 | cannabis smoking/ | 1600 | Advanced |
| 5 | tetracannabinol*.mp. | 3 | Advanced |
| 6 | or/1-5 | 40830 | Advanced |
| 7 | multiple sclerosis/ | 70086 | Advanced |
| 8 | spasticity/ | 13811 | Advanced |
| 9 | exp migraine/ | 40491 | Advanced |
| 10 | glioblastoma/ | 30377 | Advanced |
| 11 | exp degenerative disease/ | 341959 | Advanced |
| 12 | exp epilepsy/ | 159694 | Advanced |
| 13 | nausea/ | 132059 | Advanced |
| 14 | exp pain/ | 728606 | Advanced |
| 15 | exp motor dysfunction/ | 476150 | Advanced |
| 16 | parkinsonism/ | 18183 | Advanced |
| 17 | dystonia/ | 14904 | Advanced |
| 18 | exp tic/ | 8690 | Advanced |
| 19 | or/7-18 | 1680188 | Advanced |
| 20 | 6 and 19 | 6157 | Advanced |
| 21 | (exp animals/ or exp animal experimentation/) not ((exp animals/ or exp animal experimentation/) and exp human/) | 4359772 | Advanced |
| 22 | 20 not 21 | 5198 | Advanced |
| 23 | limit 22 to (book or book series or conference abstract or conference paper or "conference review" or note or conference proceeding or report) | 884 | Advanced |
| 24 | 22 not 23 | 4314 | Advanced |

| | | | |
|---|---|---|---|
| 25 | limit 24 to english language | 3905 | Advanced |
| 26 | limit 25 to embase | 3581 | Advanced |
| 27 | limit 26 to yr="2011 -Current" | 674 | Advanced |
| 28 | (2011* or 2012* or 2013*).em. | 2429701 | Advanced |
| 29 | 26 and 28 | 781 | Advanced |

***EMBASE updated November 22, 2013***

Embase 1974 to 2013 November 22

| # | Searches | Results | Search Type |
|---|---|---|---|
| 1 | exp cannabinoid/ | 42753 | Advanced |
| 2 | cannabis/ | 22886 | Advanced |
| 3 | Cannabaceae/ | 50 | Advanced |
| 4 | cannabis smoking/ | 1887 | Advanced |
| 5 | tetracannabinol*.mp. | 3 | Advanced |
| 6 | or/1-5 | 43834 | Advanced |
| 7 | multiple sclerosis/ | 75921 | Advanced |
| 8 | spasticity/ | 14951 | Advanced |
| 9 | exp migraine/ | 42817 | Advanced |
| 10 | glioblastoma/ | 34209 | Advanced |
| 11 | exp degenerative disease/ | 369487 | Advanced |
| 12 | exp epilepsy/ | 171657 | Advanced |
| 13 | nausea/ | 142033 | Advanced |
| 14 | exp pain/ | 792898 | Advanced |
| 15 | exp motor dysfunction/ | 510342 | Advanced |
| 16 | parkinsonism/ | 19504 | Advanced |
| 17 | dystonia/ | 16102 | Advanced |
| 18 | exp tic/ | 9333 | Advanced |
| 19 | or/7-18 | 1811746 | Advanced |
| 20 | 6 and 19 | 6719 | Advanced |
| 21 | (exp animals/ or exp animal experimentation/) not ((exp animals/ or exp animal experimentation/) and exp human/) | 4518731 | Advanced |
| 22 | 20 not 21 | 5676 | Advanced |
| 23 | limit 22 to (book or book series or conference abstract or conference paper or "conference review" or note or conference proceeding or report) | 1027 | Advanced |
| 24 | 22 not 23 | 4649 | Advanced |
| 25 | limit 24 to english language | 4224 | Advanced |
| 26 | limit 25 to yr="2013 -Current" | 273 | Advanced |

| | | | |
|---|---|---|---|
| 27 | 2013*.em. | 1438642 | Advanced |
| 28 | 25 and 27 | 347 | Advanced |
| 29 | 26 or 28 | 349 | Advanced |
| 30 | limit 29 to embase | 322 | Advanced |

***Web of Science updated January 25, 2013***

Search History

| Set | Results | |
|---|---|---|
| # 7 | 648 | #4 AND #1<br>Refined by: Document Types=( ARTICLE OR REVIEW ) AND Languages=( ENGLISH )<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 6 | 665 | #4 AND #1<br>Refined by: Document Types=( ARTICLE OR REVIEW )<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 5 | 714 | #4 AND #1<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 4 | 113,691 | #3 OR #2<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 3 | 78,017 | Topic=(Nausea OR pain* OR (Movement SAME Disorder?) OR Parkinson* OR Dystonia* OR Huntington* OR Tourette*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 2 | 42, 179 | Topic=("Multiple Sclerosis*" OR Spasticity* OR Migraine* OR Tic OR Glioblastoma OR Neurodegenerat* OR Heredodegenerat* OR Epilepsy*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |
| # 1 | 5,264 | Topic=(Cannab* OR Endocannab* OR Tetrahydrocannab* OR Tetracannab* OR Mari?uana*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2011-01-01 - 2013-01-25 |

***Web of Science updated November 27, 2013***

Search History

| Set | Results | |
|---|---|---|
| # 7 | 269 | #4 AND #1<br>Refined by: Document Types=( ARTICLE OR REVIEW ) AND Languages=( ENGLISH )<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 6 | 272 | #4 AND #1<br>Refined by: Document Types=( ARTICLE OR REVIEW )<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 5 | 298 | #4 AND #1<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 4 | 47,508 | #3 OR #2<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 3 | 32,435 | Topic=(Nausea OR pain* OR (Movement SAME Disorder?) OR Parkinson* OR Dystonia* OR Huntington* OR Tourette*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 2 | 17,882 | Topic=("Multiple Sclerosis*" OR Spasticity* OR Migraine* OR Tic OR Glioblastoma OR Neurodegenerat* OR Heredodegenerat* OR Epilepsy*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |
| # 1 | 2,224 | Topic=(Cannab* OR Endocannab* OR Tetrahydrocannab* OR Tetracannab* OR Mari?uana*)<br>Databases=SCI-EXPANDED, SSCI, A&HCI<br>Timespan=2013 |

***Scopus updated January 25, 2013***

- 7
- #6 AND NOT PMID(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
- 372

- 6
- #5 (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011)) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "re")) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(SRCTYPE, "j"))
- 953

- 5
- #1 AND #4
- 6, 348

- 4
- #2 OR #3
- 1,354,392

- 3
- TITLE-ABS-KEY(nausea OR pain* OR (movement W/2 disorder*) OR parkinson* OR dystonia* OR huntington* OR tourette*)
- 1, 044,211

- 2
- TITLE-ABS-KEY("Multiple Sclerosis*" OR spasticity* OR migraine* OR tic OR glioblastoma OR neurodegenerat* OR heredodegenerat* OR epilepsy*)
- 365,120

- 1
- TITLE-ABS-KEY(cannab* OR endocannab* OR tetrahydrocannab* OR tetracannab* OR marijuana* OR maihuana*)
- 48,749

***Scopus updated November 28, 2013***

- 7
- #6 AND NOT PMID(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
- 260

- 6
- #5 (LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013)) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "re")) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(SRCTYPE, "j"))
- 406

- 5
- #1 AND #4
- 6, 890

- 4
- #2 OR #3
- 1,445,614

- 3
- TITLE-ABS-KEY(nausea OR pain* OR (movement W/2 disorder*) OR parkinson* OR dystonia* OR huntington* OR tourette*)
- 1, 115,125

- 2
- TITLE-ABS-KEY("Multiple Sclerosis*" OR spasticity* OR migraine* OR tic OR glioblastoma OR neurodegenerat* OR heredodegenerat* OR epilepsy*)
- 390,400

- 1
- TITLE-ABS-KEY(cannab* OR endocannab* OR tetrahydrocannab* OR tetracannab* OR marijuana* OR maihuana*)
- 52,057

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