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| Medicinal Cannabis research update |
| September 2020 |

Foreword

The Office of Medicinal Cannabis provides quarterly updates on current research evaluating the therapeutic potential of medicinal cannabis. This research update contains summaries of significant, peer reviewed journal articles relating to medicinal cannabis that were published between June 2017 and September 2020.

The articles included in this update have not been evaluated by subject matter experts and should be used as a complement to other reliable sources of information. The Office of Medicinal Cannabis does not endorse or give assurances as to the quality of the articles contained within this update.

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# Addiction

**2020**

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# Adverse effects and safety

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# Cognition

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# Epilepsy

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Good, P., A. Haywood, et al. (2019). "Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD)." BMC Palliative Care 18(1): 110.

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# Sleep

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Suraev, A., R. R. Grunstein, et al. (2020). "Cannabidiol (CBD) and Δ(9)-tetrahydrocannabinol (THC) for chronic insomnia disorder ('CANSLEEP' trial): protocol for a randomised, placebo-controlled, double-blinded, proof-of-concept trial." BMJ Open **10**(5): e034421.

**2019**

Shannon, S., N. Lewis, et al. (2019). "Cannabidiol in Anxiety and Sleep: A Large Case Series." The Permanente journal **23**: 18-041.

**2017**

Cranford, J. A., J. T. Arnedt, et al. (2017). "Prevalence and correlates of sleep-related problems in adults receiving medical cannabis for chronic pain." Drug and alcohol dependence **180**: 227-233.

Linares, I. M. P., J. A. S. Crippa, et al. (2017). Chapter 91 - Beneficial Effects of Cannabis and Related Compounds on Sleep A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 877-882

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Abalo, R. and M. I. Martín-Fontelles (2017). Chapter 45 - Cannabis, Cannabinoids, and Visceral Pain A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 439-449.

Abstract Visceral pain is a frequent cause of seeking medical attention, and it displays distinct anatomical and functional features that make it particularly difficult to manage. The endocannabinoid system (ECS) expression is frequently upregulated in painful viscera and its innervation, particularly under chronic inflammatory conditions or cancer. Pancreatitis, endometriosis, gastritis, irritable bowel syndrome, irritable bowel disease, lower tract urinary symptoms, and painful syndromes affecting the gonads may benefit from treatment with cannabinoid agonists (particularly of type 2 receptors, CB2R), or inhibitors of endocannabinoid degradation. Clinical research will definitely determine the usefulness of these new strategies to treat visceral pain.

Abdallah, F. W., N. Hussain, et al. (2020). "Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis." Reg Anesth Pain Med **45**(7): 509-519.

BACKGROUND: Evidence regarding the role of cannabinoids in managing acute postoperative pain is conflicting. The purpose of this systematic review and meta-analysis was to determine the analgesic efficacy of perioperative cannabinoid compounds for acute pain management after surgery. METHODS: Original research articles evaluating the addition of cannabinoids to standard opioid-based systemic analgesia (Control) in the postoperative period were sought. Our primary outcomes were cumulative oral morphine equivalent consumption and rest pain severity at 24 hours postoperatively. We also assessed analgesic consumption in the postanesthesia care unit (PACU), pain scores in PACU, 6 and 12 hours postoperatively, and opioid-related and cannabinoid-related side effects, patient satisfaction, and quality of recovery as secondary outcomes. RESULTS: Eight randomized controlled trials (924 patients) and four observational studies (4259 patients) were analyzed and included. There were insufficient data to pool for quantification of differences in cumulative oral morphine equivalent consumption and rest pain severity at 24 hours postoperatively with the addition of cannabinoids in comparison to Control. Qualitative synthesis revealed no differences in cumulative oral opioid consumption or pain at rest 24 hours postoperatively with the addition of cannabinoids in comparison to Control. Patients receiving cannabinoids appeared to have an increased weighted mean difference 95% CI of pain at 12 hours by 0.83 cm (0.04 to 1.63) (p=0.04). Patients receiving cannabinoids also appeared to have 3.24 times increased odds of developing hypotension postoperatively (95% CI 1.12 to 9.36) (p=0.03). Qualitative and quantitative synthesis revealed no differences in any other secondary outcomes. CONCLUSIONS: Our quantitative and qualitative review of the literature suggests that the analgesic role of perioperative cannabinoid compounds is limited, with no clinically important benefits detected when cannabinoids are added to traditional systemic analgesics compared with traditional systemic analgesics alone. Notably, there appears to be a signal towards increased postoperative pain and hypotension associated with the addition of perioperative cannabinoids to traditional systemic analgesics. These results do not support the routine use of cannabinoids to manage acute postoperative pain at the present time.

Abi-Jaoude, E., L. Chen, et al. (2017). "Preliminary Evidence on Cannabis Effectiveness and Tolerability for Adults With Tourette Syndrome." The Journal of Neuropsychiatry and Clinical Neurosciences **29**(4): 391-400.

The authors retrospectively evaluated effectiveness and tolerability of cannabis in 19 adults with Tourette syndrome. Tics scores decreased by 60%, and 18 of the 19 participants were at least ?much improved.? Cannabis was generally well tolerated, although most participants reported side effects.

Abrams, D. I. (2018). "The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report." European Journal of Internal Medicine **49**: 7-11.

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

Abrams, D. I., P. Couey, et al. (2020). "Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial." JAMA network open **3**(7): e2010874-e2010874.

IMPORTANCE: Sickle cell disease (SCD) is characterized by chronic pain and episodic acute pain caused by vasoocclusive crises, often requiring high doses of opioids for prolonged periods. In humanized mouse models of SCD, a synthetic cannabinoid has been found to attenuate both chronic and acute hyperalgesia. The effect of cannabis on chronic pain in adults with SCD is unknown. OBJECTIVE: To determine whether inhaled cannabis is more effective than inhaled placebo in relieving chronic pain in adults with SCD. DESIGN, SETTING, AND PARTICIPANTS: This pilot randomized clinical trial included participants with SCD with chronic pain admitted to a single inpatient clinical research center for 2 separate 5-day stays from August 2014 to April 2017. Participants inhaled either vaporized cannabis (4.4% Δ-9-tetrahydrocannabinol to 4.9% cannabidiol) 3 times daily or vaporized placebo cannabis. Pain and pain interference ratings using the Brief Pain Inventory were assessed throughout each 5-day period. Participants with SCD and chronic pain on stable analgesics were eligible to enroll. A total of 90 participants were assessed for eligibility; 56 participants were deemed ineligible, and 34 participants were enrolled. Of these, 7 participants dropped out before randomization. Of 27 randomized participants, 23 completed both treatment arms of the crossover study and were included in the final per protocol analysis. Data analysis was completed in June 2019, with the sensitivity analysis conducted in April 2020. INTERVENTIONS: Inhalation of vaporized cannabis plant (4.4% Δ-9-tetrahydrocannbinol to 4.9% cannabidiol) or placebo cannabis plant using a vaporizer 3 times daily for 5 days. MAIN OUTCOMES AND MEASURES: Daily pain assessed with visual analog scale and Brief Pain Inventory. RESULTS: A total of 23 participants (mean [SD] age, 37.6 [11.4] years; 13 [56%] women) completed the trial. The mean (SD) difference in pain rating assessment between the cannabis and placebo groups was -5.3 (8.1) for day 1, -10.9 (7.0) for day 2, -16.5 (9.2) for day 3, -8.9 (6.7) for day 4, and -8.2 (8.1) for day 5; however, none of these differences were statistically significant. There was no statistically significant mean (SD) difference in pain interference ratings between cannabis and placebo between days 1 and 5 for interference in general activities (day 1: 0.27 [0.35]; day 5: -1.0 [0.5]), walking (day 1: 0.14 [0.73]; day 5: -0.87 [0.63]), sleep (day 1: 0.59 [0.74]; day 5: -1.3 [0.8]), or enjoyment (day 1: 0.23 [0.69]; day 5: -0.91 [0.48]), but there was a statistically significant mean (SD) difference in decrease in interference with mood (day 1: 0.96 [0.59]; day 5: -1.4 [0.6]; P = .02). No differences in treatment-related adverse effects were observed. Use of concomitant opioids was similar during both treatment periods. CONCLUSIONS AND RELEVANCE: This randomized clinical trial found that, compared with vaporized placebo, vaporized cannabis did not statistically significantly reduce pain and associated symptoms, except interference in mood, in patients with SCD with chronic pain. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01771731.

Abuhasira, R., A. Ron, et al. (2019). "Medical Cannabis for Older Patients-Treatment Protocol and Initial Results." J Clin Med 8(11).

Older adults may benefit from cannabis treatment for various symptoms such as chronic pain, sleep difficulties, and others, that are not adequately controlled with evidence-based therapies. However, currently, there is a dearth of evidence about the efficacy and safety of cannabis treatment for these patients. This article aims to present a pragmatic treatment protocol for medical cannabis in older adults. We followed consecutive patients above 65 years of age prospectively who were treated with medical cannabis from April 2017 to October 2018. The outcomes included treatment adherence, global assessment of efficacy and adverse events after six months of treatment. During the study period, 184 patients began cannabis treatment, 63.6% were female, and the mean age was 81.2 +/- 7.5 years (median age-82). After six months of treatment, 58.1% were still using cannabis. Of these patients, 33.6% reported adverse events, the most common of which were dizziness (12.1%) and sleepiness and fatigue (11.2%). Of the respondents, 84.8% reported some degree of improvement in their general condition. Special caution is warranted in older adults due to polypharmacy, pharmacokinetic changes, nervous system impairment, and increased cardiovascular risk. Medical cannabis should still be considered carefully and individually for each patient after a risk-benefit analysis and followed by frequent monitoring for efficacy and adverse events.

Abuhasira, R., L. B.-L. Schleider, et al. (2018). "Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly." European Journal of Internal Medicine **49**: 44-50.

Introduction There is a substantial growth in the use of medical cannabis in recent years and with the aging of the population, medical cannabis is increasingly used by the elderly. We aimed to assess the characteristics of elderly people using medical cannabis and to evaluate the safety and efficacy of the treatment. Methods A prospective study that included all patients above 65 years of age who received medical cannabis from January 2015 to October 2017 in a specialized medical cannabis clinic and were willing to answer the initial questionnaire. Outcomes were pain intensity, quality of life and adverse events at six months. Results During the study period, 2736 patients above 65 years of age began cannabis treatment and answered the initial questionnaire. The mean age was 74.5 ± 7.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0–10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose. Conclusion Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative.

Abu-Sawwa, R., B. Scutt, et al. (2020). "Emerging Use of Epidiolex (Cannabidiol) in Epilepsy." The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG **25**(6): 485-499.

The first plant-derived, purified pharmaceutical-grade cannabidiol (CBD) medication, Epidiolex, was approved in the United States by the FDA on June 25, 2018. Its approval for patients ≥ 2 years of age with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) markedly altered the treatment of medically refractory seizures in these disorders. This state-of-the-art review will discuss the history of CBD, its current pharmacology and toxicology, evidence supporting its use in a variety of epileptic syndromes, common side effects and adverse effects, and pharmacokinetically based drug-drug interactions. Owing to the importance in considering side effects, adverse effects, and drug-drug interactions in patients with medically refractory epilepsy syndromes, this review will take a deeper look into the nuances of the above within a clinical context, as compared to the other antiepileptic medications. Furthermore, despite the limited data regarding clinically significant drug-drug interactions, potential pharmacokinetic drug-drug interactions with CBD and other antiepileptics are theorized on the basis of their metabolic pathways. The article will further elucidate future research in terms of long-term efficacy, safety, and drug interactions that is critical to addressing unanswered questions relevant to clinical practice.

Afrin, F., M. Chi, et al. (2020). "Can Hemp Help? Low-THC Cannabis and Non-THC Cannabinoids for the Treatment of Cancer." Cancers **12**(4): 1033.

Cannabis has been used to relieve the symptoms of disease for thousands of years. However, social and political biases have limited effective interrogation of the potential benefits of cannabis and polarised public opinion. Further, the medicinal and clinical utility of cannabis is limited by the psychotropic side effects of ∆(9)-tetrahydrocannabinol (∆(9)-THC). Evidence is emerging for the therapeutic benefits of cannabis in the treatment of neurological and neurodegenerative diseases, with potential efficacy as an analgesic and antiemetic for the management of cancer-related pain and treatment-related nausea and vomiting, respectively. An increasing number of preclinical studies have established that ∆(9)-THC can inhibit the growth and proliferation of cancerous cells through the modulation of cannabinoid receptors (CB1R and CB2R), but clinical confirmation remains lacking. In parallel, the anti-cancer properties of non-THC cannabinoids, such as cannabidiol (CBD), are linked to the modulation of non-CB1R/CB2R G-protein-coupled receptors, neurotransmitter receptors, and ligand-regulated transcription factors, which together modulate oncogenic signalling and redox homeostasis. Additional evidence has also demonstrated the anti-inflammatory properties of cannabinoids, and this may prove relevant in the context of peritumoural oedema and the tumour immune microenvironment. This review aims to document the emerging mechanisms of anti-cancer actions of non-THC cannabinoids.

Alessandria, G., R. Meli, et al. (2020). "Long-term assessment of the cognitive effects of nabiximols in patients with multiple sclerosis: A pilot study." Clinical Neurology and Neurosurgery **196**: 105990.

Objective Moderate to severe spasticity is commonly reported in Multiple Sclerosis (MS) and its management is still a challenge. Cannabinoids were recently suggested as add-on therapy for the treatment of spasticity and chronic pain in MS but there is no conclusive scientific evidence on their safety, especially on cognition and over long periods. The aim of this prospective pilot study was to assess the long-term effects of a tetrahydrocannabinol-cannabidiol (THC/CBD) oromucosal spray (Sativex®) on cognition, mood and anxiety. Patients and Methods An extensive and specific battery of neuropsychological tests (Symbol Digit Modalities Test-SDMT, California Verbal Learning Test-CVLT, Brief Visuospatial Memory Test-BVMT; PASAT-3 and 2; Free and Cued Selective Remind Test-FCSRT, Index of Sensitivity of Cueing-ISC) was applied to longitudinally investigate different domains of cognition in 20 consecutive MS patients receiving Sativex for spasticity. The primary endpoint was to assess any variation in cognitive performance. Secondary outcomes regarding mood and anxiety were investigated by means of Beck Depression Inventory (BDI) and Hamilton Anxiety Rating Scale (HAM-A). Any change in patients’ spasticity was evaluated using the 0–10 Numerical Rating Scale (NRS). Results Twenty per protocol patients were followed up and evaluated at baseline, 6 and 12 months. Domains involving processing speed and auditory verbal memory significantly improved within the first 6 months of therapy (SDMT: p < 0.001; CVLT: p = 0.0001). Mood and anxiety did not show any significant variation. Additionally, the NRS score significantly improved since the beginning (p < 0.0001). Conclusions These results are encouraging in supporting possible long-term benefits of Sativex on cognition and a wider role than symptom alleviator. Further studies on larger groups of patients would be necessary in order to test this intriguing possibility.

Alexander, S. P. (2020). "Barriers to the wider adoption of medicinal Cannabis." Br J Pain **14**(2): 122-132.

The use of Cannabis-based preparations for medicinal use has waxed and waned in the multi-millennial history of human co-existence with the plant and its cultivation. Recorded use of preparations from Cannabis is effectively as old as recorded history with examples from China, India and Ancient Egypt. Prohibition and restriction of availability allowed a number of alternatives to take the place of Cannabis preparations. However, there has been a worldwide resurgence in medicinal Cannabis advocacy from the public. Media interest has been piqued by particular evocative cases. Altogether, therefore, there is pressure on healthcare professionals to prescribe and dispense Cannabis-based preparations. This review enunciates some of the barriers which are slowing the wider adoption of medicinal Cannabis.

Ali, S., I. E. Scheffer, et al. (2018). "Efficacy of cannabinoids in paediatric epilepsy." Developmental Medicine & Child Neurology **61**(1): 13-18.

There are hundreds of compounds found in the marijuana plant, each contributing differently to the antiepileptic and psychiatric effects. Cannabidiol (CBD) has the most evidence of antiepileptic efficacy and does not have the psychoactive effects of ?9-tetrahydrocannabinol. CBD does not act via cannabinoid receptors and its antiepileptic mechanism of action is unknown. Despite considerable community interest in the use of CBD for paediatric epilepsy, there has been little evidence for its use apart from anecdotal reports, until the last year. Three randomized, placebo-controlled, double-blind trials in Dravet syndrome and Lennox?Gastaut syndrome found that CBD produced a 38% to 41% median reduction in all seizures compared to 13% to 19% on placebo. Similarly, CBD resulted in a 39% to 46% responder rate (50% convulsive or drop-seizure reduction) compared to 14% to 27% on placebo. CBD was well tolerated; however, sedation, diarrhoea, and decreased appetite were frequent. CBD shows similar efficacy to established antiepileptic drugs. What this paper adds Cannabidiol (CBD) shows similar efficacy in the severe paediatric epilepsies to other antiepileptic drugs. Careful down-titration of benzodiazepines is essential to minimize sedation with adjunctive CBD.

Allison, D., A. Agudelo, et al. (2020). "Cannabinoids and an anti-inflammatory diet for the treatment of neuropathic pain after spinal cord injury (The CATNP Study): study protocol for a randomized controlled trial." Spinal Cord: 1-11.

Multicenter, randomized, double-blind, placebo controlled, clinical trial. The objective of this paper is to evaluate the effectiveness of cannabinoids and an anti-inflammatory diet, alone and in combination, for the management of neuropathic pain (NP) after spinal cord injury (SCI). Two Canadian SCI rehabilitation centers. A sample of 144 individuals with SCI will receive either an anti-inflammatory diet, cannabinoids or a placebo for 6 weeks. Following this, a combined effect of these treatments will be evaluated for a further 6 weeks. The primary outcome measure will be the change in NP as assessed by the numeric rating scale (NRS). Secondary outcomes will include changes in inflammation, mood, sleep, spasticity, cost-effectiveness, and function. This study will assess the efficacy of an anti-inflammatory diet and cannabinoids (individually and in combination) for the treatment of NP following SCI. Results may reveal a cost-effective, side-effect free intervention strategy which could be utilized for the long-term management of NP following SCI.

Almogi-Hazan, O., I. Khuja, et al. (2020). "The Highs and Lows of Cannabis in Cancer Treatment and Bone Marrow Transplantation." Rambam Maimonides Med J **11**(1).

In the last decade, we have observed an increased public and scientific interest in the clinical applications of medical cannabis. Currently, the application of cannabinoids in cancer patients is mainly due to their analgesic and anti-emetic effects. The direct effects of phyto-cannabinoids on cancer cells are under intensive research, and the data remain somewhat inconsistent. Although anti-proliferative properties were observed in vitro, conclusive data from animal models and clinical trials are lacking. Since immunotherapy of malignant diseases and bone marrow transplantation are integral approaches in hemato-oncology, the immuno-modulatory characteristic of cannabinoids is a fundamental aspect for consideration. The effect of cannabinoids on the immune system is presently under investigation, and some evidence for its immuno-regulatory properties has been shown. In addition, the interaction of cannabinoids and classical cytotoxic agents is a subject for further investigation. Here we discuss the current knowledge of cannabinoid-based treatments in preclinical models and the limited data in oncological patients. Particularly, we address the possible contradiction between the direct anti-tumor and the immune-modulatory effects of cannabinoids. Better understanding of the mechanism of cannabinoids influence is essential to design therapies that will allow cannabinoids to be incorporated into the clinic.

Almog, S., J. Aharon-Peretz, et al. (2020). "The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial." European Journal of Pain **n/a**(n/a).

Abstract Background Precise cannabis treatment dosing remains a major challenge, leading to physicians? reluctance to prescribe medical cannabis. Objective To test the pharmacokinetics, analgesic effect, cognitive performance and safety effects of an innovative medical device that enables the delivery of inhaled therapeutic doses of ?9-Tetrahydrocannabinol (THC) in patients with chronic pain. Methods In a randomized, three-arms, double-blinded, placebo-controlled, cross-over trial, 27 patients received a single inhalation of ?9-THC: 0.5mg, 1mg, or a placebo. ?9-THC plasma levels were measured at baseline and up to 150-min post-inhalation. Pain intensity and safety parameters were recorded on a 10-cm visual analogue scale (VAS) at pre-defined time points. The cognitive performance was evaluated using the selective sub-tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Results Following inhalation of 0.5 mg or 1mg, ?9-THC plasma Cmax ± SD were 14.3 ± 7.7 and 33.8 ± 25.7 ng/ml. Tmax ± SD were 3.7 ± 1.4 and 4.4 ± 2.1 min, and AUC0 ? infinity±SD were 300 ± 144 and 769 ± 331 ng\*min/ml, respectively. Both doses, but not the placebo, demonstrated a significant reduction in pain intensity compared with baseline and remained stable for 150-min. The 1-mg dose showed a significant pain decrease compared to the placebo. Adverse events were mostly mild and resolved spontaneously. There was no evidence of consistent impairments in cognitive performance. Conclusion This feasibility trial demonstrated that a metered-dose cannabis inhaler delivered precise and low THC doses, produced a dose-dependent and safe analgesic effect in patients with neuropathic pain/ complex-regional pain syndrome (CRPS). Thus, it enables individualization of medical cannabis regimens that can be evaluated pharmacokinetically and pharmacodynamically by accepted pharmaceutical models. Significance Evidence suggests that cannabis-based medicines are an effective treatment for chronic pain in adults. The pharmacokinetics of THC varies as a function of its route of administration. Pulmonary assimilation of inhaled THC causes rapid onset of analgesia. However, currently used routes of cannabinoids delivery provide unknown doses, making it impossible to implement a pharmaceutical standard treatment plan. A novel selective-dose cannabis inhaler delivers significantly low and precise doses of THC, thus allowing the administration of inhaled cannabis-based medicines according to high pharmaceutical standards. These low doses of THC can produce safe and effective analgesia in patients with chronic pain.

Alshaarawy, O. and H. A. Elbaz (2016). "Cannabis Use and Blood Pressure Levels: United States National Health and Nutrition Examination Survey, 2005–2012." Journal of hypertension **34**(8): 1507-1512.

OBJECTIVE: Pre-clinical studies have reported acute cardiovascular effects of cannabis including a dose-dependent increase in blood pressure while orthostatic hypotension may follow as a result of decreased vascular resistance. In case reports, evidence links cannabis with acute cardiovascular events in young and middle aged adults. Here, we offer epidemiologic estimates on cannabis use-blood pressure levels association from the United States (US) National Health and Nutrition Examination Surveys 2005–2012 (n=12426). METHODS: Computer-assisted self-interviews assessed cannabis use. Blood pressure was determined by an average of up to four measurements taken during a single examination. Regression modeling was used to examine cannabis use– blood pressure association. RESULTS: Recently active cannabis use was associated with increase in systolic blood pressure (β = 1.6; 95% CI: 0.6, 2.7) in the age-sex adjusted model. Additional covariate adjustment did not affect the positive association. No association between cannabis use and diastolic blood pressure was detected. CONCLUSION: A modest association between recent cannabis use and systolic blood pressure was detected among a relatively large nationally representative sample of US adults. With the legalization of cannabis, there a need for pre-clinical, clinical and prospective population-based research on the cardiovascular effects of cannabis use.

Alsherbiny, M. A. and C. G. Li (2018). "Medicinal Cannabis-Potential Drug Interactions." Medicines (Basel) **6**(1).

The endocannabinoids system (ECS) has garnered considerable interest as a potential therapeutic target in various carcinomas and cancer-related conditions alongside neurodegenerative diseases. Cannabinoids are implemented in several physiological processes such as appetite stimulation, energy balance, pain modulation and the control of chemotherapy-induced nausea and vomiting (CINV). However, pharmacokinetics and pharmacodynamics interactions could be perceived in drug combinations, so in this short review we tried to shed light on the potential drug interactions of medicinal cannabis. Hitherto, few data have been provided to the healthcare practitioners about the drug(-)drug interactions of cannabinoids with other prescription medications. In general, cannabinoids are usually well tolerated, but bidirectional effects may be expected with concomitant administered agents via affected membrane transporters (Glycoprotein p, breast cancer resistance proteins, and multidrug resistance proteins) and metabolizing enzymes (Cytochrome P450 and UDP-glucuronosyltransferases). Caution should be undertaken to closely monitor the responses of cannabis users with certain drugs to guard their safety, especially for the elderly and people with chronic diseases or kidney and liver conditions.

Amanda Reiman, Mark Welty, and Perry Solomon "Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report." Cannabis and Cannabinoid Research **Volume 2.1, 2017**: 160 - 166.

Introduction: Prescription drug overdoses are the leading cause of accidental death in the United States. Alternatives to opioids for the treatment of pain are necessary to address this issue. Cannabis can be an effective treatment for pain, greatly reduces the chance of dependence, and eliminates the risk of fatal overdose compared to opioid-based medications. Medical cannabis patients report that cannabis is just as effective, if not more, than opioid-based medications for pain. Materials and Methods: The current study examined the use of cannabis as a substitute for opioid-based pain medication by collecting survey data from 2897 medical cannabis patients. Discussion: Thirty-four percent of the sample reported using opioid-based pain medication in the past 6 months. Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects. Ninety-seven percent of the sample ‘‘strongly agreed/agreed’’ that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% ‘‘strongly agreed/agreed’’ that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. Results were similar for those using cannabis with nonopioid-based pain medications. Conclusion: Future research should track clinical outcomes where cannabis is offered as a viable substitute for pain treatment and examine the outcomes of using cannabis as a medication assisted treatment for opioid dependence.

Ananth, P., C. Ma, et al. (2017). "Provider Perspectives on Use of Medical Marijuana in Children With Cancer." Pediatrics.

BACKGROUND: Although medical marijuana (MM) may have utility in the supportive care of children with serious illness, it remains controversial. We investigated interdisciplinary provider perspectives on legal MM use in children with cancer.METHODS: We sent a 32-item, cross-sectional survey to 654 pediatric oncology providers in Illinois, Massachusetts, and Washington characterizing MM practices, knowledge, attitudes, and barriers. Forty-eight percent responded; 44% (n = 288) were included in analyses. Providers were stratified by status as legally eligible to certify (ETC) for MM. We used Fisher’s exact and Wilcoxon rank tests and univariate and multivariate logistic regression models for group comparisons.RESULTS: The provider median age was 35 years (range 22–70 years); 33% were ETC (83 physicians; 13 Washington state advance practice providers). Thirty percent of providers received ≥1 request for MM in the previous month. Notably, only 5% of all providers knew state-specific regulations. ETC providers were more likely to know that MM is against federal laws (P &amp;lt; .0001). Whereas most providers (92%) reported willingness to help children with cancer access MM, in adjusted models, ETC providers were less likely to indicate approval of patient MM use by smoking, oral formulations, as cancer-directed therapy, or to manage symptoms (P &amp;lt; .005 for all). Forty-six percent of all providers cited the absence of standards around formulations, potency, or dosing to be the greatest barrier to recommending MM.CONCLUSIONS: Most pediatric oncology providers are willing to consider MM use in children with cancer and receive frequent inquiries. However, ETC providers endorse less favorable attitudes overall. The absence of standards is an important barrier to recommending MM.

Anderson, S. P., D. M. Zylla, et al. (2019). "Impact of Medical Cannabis on Patient-Reported Symptoms for Patients With Cancer Enrolled in Minnesota’s Medical Cannabis Program." Journal of Oncology Practice 15(4): e338-e345.

PURPOSE:Minnesota?s medical cannabis program is unique, in that it routinely collects patient-reported scores on symptoms. This article focuses on changes in symptom severity reported by patients with cancer during their first 4 months of program participation.MATERIALS AND METHODS:Patients with cancer in Minnesota?s medical cannabis program reported symptoms (anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, pain, and vomiting) at their worst over the last 24 hours before each medical cannabis purchase. Baseline scores on each of the eight symptoms were statistically compared with the average symptom scores reported in the first 4 months of program participation. Symptom scores were also calculated as percent change from baseline, with patients achieving and maintaining at least a 30% reduction in symptoms reported in this article. Patients also reported intensity of adverse effects.RESULTS:A significant reduction in scores was found across all symptoms when comparing baseline scores with the average score submitted within the first 4 months of program participation (all Ps < .001). The proportion of patients achieving 30% or greater symptom reduction within the first 4 months of program participation varied from 27% (fatigue) to 50% (vomiting), with a smaller proportion both achieving and maintaining those improvements. Adverse effects were reported in a small proportion of patients (10.5%).CONCLUSION:Patients with cancer enrolled in Minnesota?s medical cannabis program showed significant reduction across all eight symptoms assessed within 4 months of program participation. Medical cannabis was well tolerated, and some patients attained clinically meaningful and lasting levels of improvement.

Aran, A. and D. Cayam-Rand (2020). "Medical Cannabis in Children." Rambam Maimonides medical journal **11**(1): e0003.

The use of medical cannabis in children is rapidly growing. While robust evidence currently exists only for pure cannabidiol (CBD) to treat specific types of refractory epilepsy, in most cases, artisanal strains of CBD-rich medical cannabis are being used to treat children with various types of refractory epilepsy or irritability associated with autism spectrum disorder (ASD). Other common pediatric disorders that are being considered for cannabis treatment are Tourette syndrome and spasticity. As recreational cannabis use during youth is associated with serious adverse events and medical cannabis use is believed to have a relatively high placebo effect, decisions to use medical cannabis during childhood and adolescence should be made with caution and based on evidence. This review summarizes the current evidence for safety, tolerability, and efficacy of medical cannabis in children with epilepsy and in children with ASD. The main risks associated with use of Δ9-tetrahydrocannabinol (THC) and CBD in the pediatric population are described, as well as the debate regarding the use of whole-plant extract to retain a possible "entourage effect" as opposed to pure cannabinoids that are more standardized and reproducible.

Arboleda, M., E. Prosk, et al. (2020). "Medical cannabis in supportive cancer care: lessons from Canada." Supportive Care in Cancer **28**.

Medical cannabis, or cannabinoid-based products, continues to grow in popularity globally, driving the evolution of regulatory access frameworks; cancer patients and caregivers often rely on guidance from their physicians regarding cannabinoid-based treatments. But the majority of healthcare practitioners still feel unprepared and insufficiently informed to make reasonable, evidence-based recommendations about medical cannabis. More than 30 countries worldwide have now legalized access to medical cannabis; yet various nations still face arduous regulatory challenges to fulfill the needs of patients, healthcare practitioners, and other medical stakeholders. This has affected the deployment of comprehensive medical cannabis access programs adapted to cultural and social realities. With a 20-year history of legal medical cannabis access and nearly 400,000 registered patients under its federal access program, Canada serves as a model for countries which are developing their regulatory frameworks. The Canadian clinical experience in cannabinoid-based treatments is also a valuable source of lessons for healthcare professionals who wish to better understand the current evidence examining medical cannabis for oncology patients.

Archie, S. R. and L. Cucullo (2019). "Harmful Effects of Smoking Cannabis: A Cerebrovascular and Neurological Perspective." Frontiers in Pharmacology 10(1481).

Apart from being used as a medicine, cannabis or marijuana is the most widely abused recreational drug all over the world. The legalization and decriminalization of cannabis in Canada and various states of USA may be the underlying reason of the widespread popularity of it among young population. Various studies have reported about the relationship between cannabis use and different detrimental effects like cardiovascular, cerebrovascular, and neurological complications among different age groups. Specifically, the young population is getting adversely affected by this, harmful yet, readily accessible recreational drug. Although the mechanism behind cannabis mediated neurological and cerebrovascular complications has not been elucidated yet, the results of these studies have confirmed the association of these diseases with cannabis. Given the lack of comprehensive study relating these harmful complications with cannabis use, the aim of this narrative literature review article is to evaluate and summarize current studies on cannabis consumption and cerebrovascular/neurological diseases along with the leading toxicological mechanisms.

Argueta, D. A., C. M. Ventura, et al. (2020). "A Balanced Approach for Cannabidiol Use in Chronic Pain." Frontiers in pharmacology **11**: 561-561.

Cannabidiol (CBD), the major non-psychoactive constituent of Cannabis sativa L., has gained traction as a potential treatment for intractable chronic pain in many conditions. Clinical evidence suggests that CBD provides therapeutic benefit in certain forms of epilepsy and imparts analgesia in certain conditions, and improves quality of life. CBD continues to be Schedule I or V on the list of controlled substances of the Drug Enforcement Agency of the United States. However, preparations labeled CBD are available publicly in stores and on the streets. However, use of CBD does not always resolve pain. CBD purchased freely entails the risk of adulteration by potentially hazardous chemicals. As well, CBD use by pregnant women is rising and poses a major health-hazard for future generations. In this mini-review, we present balanced and unbiased pre-clinical and clinical findings for the beneficial effects of CBD treatment on chronic pain and its deleterious effects on prenatal development.

Arnfinsen, J. and A. Kisa (2020). "Assessment of Norwegian physicians' knowledge, experience and attitudes towards medical cannabis." Drugs: Education Prevention and Policy.

Background Medicinal cannabis (MC) has been used extensively throughout history. However, its criminalization in the United States in 1937 spurred the international community to follow suit, including Norway. Despite being reintroduced as a medical treatment in many countries in recent years, the use of MC in Norway is confined to a select few patient groups, and medical specialists must formally apply for authorization from the Norwegian authorities to prescribe the drug. Objective To assess Norwegian physicians’ perceived knowledge of, experience with, and attitudes towards MC. Methods A cross-sectional survey consisting of 31 closed-ended items captured physicians’ perceived knowledge of, experience with, and attitudes towards this treatment. Results A total of 102 physicians participated in this study. Physicians generally agreed that MC is a legitimate treatment option (n = 45, 44.1%), that it represents a therapeutic agent for treating cancer and chemotherapy-induced side effects (n = 88, 86%), and that it has the potential to reduce unnecessary opioid use in patients with chronic pain (n = 40, 39.2%). Statistically significant differences were found between subgroups in the sample in terms of years of practice, specialty, age, country the medical diploma was obtained from, and practice type. Conclusions This study found acceptance of cannabis as a therapeutic agent as well as acceptance towards MC being introduced by prescription in Norway. Further large-scale in-depth studies on provider perspectives towards MC are warranted.

Arora, K., S. H. Qualls, et al. (2019). "Measuring Attitudes Toward Medical and Recreational Cannabis Among Older Adults in Colorado." The Gerontologist **60**(4): e232-e241.

Cannabis use among older adults is on the rise. Despite growing interest in the topic, there exists a paucity of standardized measures capturing cannabis-specific attitudes among older adults. Using data from a survey of older Coloradans, we create two scales that separately measure medical and recreational cannabis attitudes. We also examine how these two attitudes relate to individual-level characteristics.We assess reliability using Cronbach’s alpha and item-rest correlations and perform confirmatory factor analyses to test the two attitude models. We conduct a seemingly unrelated regression estimation to assess how individual characteristics predict medical and recreational cannabis attitude scores.Twelve indicators combined into two valid and reliable scales. Both scales had a three-factor structure with affect, cognition and social perception as latent dimensions. For both scales, fit indices for the three-factor model were statistically superior when compared with other models. The three-factor structure for both scales was invariant across age groups. Age, physical health, and being a caregiver differentially predicted medical and recreational cannabis attitude scores.Medical and recreational cannabis attitude scales can inform the development and evaluation of tailored interventions targeting older adult attitudes that aim to influence cannabis use behaviors. These scales also enable researchers to measure cannabis-specific attitudes among older adults more accurately and parsimoniously, which in turn can facilitate a better understanding of the complex interplay between cannabis policy, use, and attitudes.

Arterberry, B. J., H. Treloar, et al. (2017). "Empirical Profiles of Alcohol and Marijuana Use, Drugged Driving, and Risk Perceptions." Journal of Studies on Alcohol and Drugs **78**(6): 889-898.

Objective:The present study sought to inform models of risk for drugged driving through empirically identifying patterns of marijuana use, alcohol use, and related driving behaviors. perceived dangerousness and consequences of drugged driving were evaluated as putative influences on risk patterns.Method:We used latent profile analysis of survey responses from 897 college students to identify patterns of substance use and drugged driving. We tested the hypotheses that low perceived danger and low perceived likelihood of negative consequences of drugged driving would identify individuals with higher-risk patterns.Results:Findings from the latent profile analysis indicated that a fourprofile model provided the best model fit. Low-level engagers had low rates of substance use and drugged driving. Alcohol-centric engagers had higher rates of alcohol use but low rates of marijuana/simultaneous use and low rates of driving after substance use. Concurrent engagers had higher rates of marijuana and alcohol use, simultaneous use, and related driving behaviors, but marijuana-centric/simultaneous engagers had the highest rates of marijuana use, co-use, and related driving behaviors. Those with higher perceived danger of driving while high were more likely to be in the low-level, alcohol-centric, or concurrent engagers? profiles; individuals with higher perceived likelihood of consequences of driving while high were more likely to be in the low-level engagers group.Conclusions:Findings suggested that college students? perceived dangerousness of driving after using marijuana had greater influence on drugged driving behaviors than alcohol-related driving risk perceptions. These results support targeting marijuana-impaired driving risk perceptions in young adult intervention programs.

Aviram, J., Y. Vysotski, et al. (2020). "Migraine Frequency Decrease Following Prolonged Medical Cannabis Treatment: A Cross-Sectional Study." Brain sciences **10**(6): 360.

BACKGROUND: Medical cannabis (MC) treatment for migraine is practically emerging, although sufficient clinical data are not available for this indication. This cross-sectional questionnaire-based study aimed to investigate the associations between phytocannabinoid treatment and migraine frequency. METHODS: Participants were migraine patients licensed for MC treatment. Data included self-reported questionnaires and MC treatment features. Patients were retrospectively classified as responders vs. non-responders (≥50% vs. <50% decrease in monthly migraine attacks frequency following MC treatment initiation, respectively). Comparative statistics evaluated differences between these two subgroups. RESULTS: A total of 145 patients (97 females, 67%) with a median MC treatment duration of three years were analyzed. Compared to non-responders, responders (n = 89, 61%) reported lower current migraine disability and lower negative impact, and lower rates of opioid and triptan consumption. Subgroup analysis demonstrated that responders consumed higher doses of the phytocannabinoid ms\_373\_15c and lower doses of the phytocannabinoid ms\_331\_18d (3.40 95% CI (1.10 to 12.00); p < 0.01 and 0.22 95% CI (0.05-0.72); p < 0.05, respectively). CONCLUSIONS: These findings indicate that MC results in long-term reduction of migraine frequency in >60% of treated patients and is associated with less disability and lower antimigraine medication intake. They also point to the MC composition, which may be potentially efficacious in migraine patients.

Azagba, S., L. Shan, et al. (2020). "Rural-urban differences in cannabis detected in fatally injured drivers in the United States." Preventive Medicine **132**: 105975.

While there is a vast literature on rural and urban differences in substance use, little is known in terms of cannabis positive drug tests among fatally injured drivers. In the present study, we examined rural-urban differences in cannabis detected in fatally-injured drivers. Data were drawn from the 2015–2017 Fatality Analysis Reporting System. Multivariable logistic regression was performed to examine rural-urban differences in the percentage of cannabis detected in fatally-injured drivers. Analyses were stratified by rural-urban classification and sex. A positive cannabis test in fatally-injured drivers was more prevalent in urban locations. Compared to fatally-injured drivers in rural locations, urban drivers had higher odds of a positive test for cannabinoids (aOR: 1.21, 95% CI 1.14–1.28). Non-Hispanic Black drivers had higher odds of testing positive for cannabinoids (aOR: 1.43, 95% CI 1.31–1.55). Those aged at least 25 years had lower odds of a positive test for cannabinoids. Drivers involved in a weekend nighttime crash (aOR: 1.14, 95% CI 1.03–1.26) and weekday nighttime (aOR: 1.15, 95% CI 1.05–1.26) had higher odds of testing positive for cannabinoids compared to drivers involved in a weekend daytime crash. Results showed significant rural-urban differences in the prevalence of cannabis detected in fatally-injured drivers.

A Thomas, A., E. Moser, et al. (2017). A Review of Pediatric Marijuana Exposure in the Setting of Increasing Legalization.

Pediatric marijuana poisonings are increasing in the United States. Signs and symptoms of marijuana exposure in pediatric patients differ throughout the pediatric age spectrum, and it is important for clinicians to be familiar with the profound lethargy or altered mental status that can occur in pediatrics, particularly in toddlers. This article reviews the clinical effects and treatment of pediatric marijuana exposure, as well as issues around legalization and prevention.

Baeeri, M., M. Rahimifard, et al. (2020). "Cannabinoids as anti-ROS in aged pancreatic islet cells." Life Sciences **256**: 117969.

Aims Cannabinoids are the chemical compounds with a high affinity for cannabinoid receptors affecting the central nervous system through the release of neurotransmitters. However, the current knowledge related to the role of such compounds in the regulation of cellular aging is limited. This study aimed to investigate the effect of cannabidiol and tetrahydrocannabinol on the function of aged pancreatic islets. Main methods The expression of p53, p38, p21, p16, and Glut2 genes and β-galactosidase activity were measured as hallmarks of cell aging applying real-time PCR, ELISA, and immunocytochemistry techniques. Pdx1 protein expression, insulin release, and oxidative stress markers were compared between young and aged rat pancreatic islet cells. Key findings Upon the treatment of aged pancreatic islets cells with cannabidiol and tetrahydrocannabinol, the expression of p53, p38, p21 and the activity of β-galactosidase were reduced. Cannabidiol and tetrahydrocannabinol increase insulin release, Pdx1, Glut2, and thiol molecules expression, while the oxidative stress parameters were decreased. The enhanced expression of Pdx1 and insulin release in aged pancreatic islet cells reflects the extension of cell healthy aging due to the significant reduction of ROS. Significance This study provides evidence for the involvement of cannabidiol and tetrahydrocannabinol in the oxidation process of cellular aging.

Bahji, A., A. Chinna Meyyappan, et al. (2020). "Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis." Journal of Psychiatric Research **129**.

Objective The aim of this study was to assess the efficacy and acceptability of cannabinoids for the treatment of anxiety disorders. Methods For this systematic review and meta-analysis, we searched for randomized trials utilizing cannabinoids for the treatment of adults with anxiety disorders. Primary outcomes were reduction in anxiety disorder symptoms, and study discontinuation due to adverse events. Evidence was synthesized as rate ratios (RRs) and as standardized mean differences (SMDs) using random-effects meta-analyses. Results A total of 14 eligible trials representing 1548 individuals (median age: 33 years; range: 28-44; 66% male) were identified. Cannabinoids reduced anxiety symptoms (SMD = -1.85, 95% CI: -2.61 to -1.09) without causing significant adverse events. Greater efficacy was observed among younger patients (p<0.01) and with longer treatment (p<0.01). However, publication bias was substantial, and after correction, the overall anxiolytic effect was not statistically significant. Conclusions While cannabinoids may be of potential value in the treatment of anxiety disorders, the routine use of these treatments is not supported by the available evidence after correction for publication bias.

Bahorik, A. L., C. I. Campbell, et al. (2018). "Adverse impact of marijuana use on clinical outcomes among psychiatry patients with depression and alcohol use disorder." Psychiatry Research **259**: 316-322.

This study examined whether marijuana use was associated with clinically problematic outcomes for patients with depression and alcohol use disorder (AUD). The sample consisted of 307 psychiatry outpatients with mild to severe depression and past 30-day hazardous drinking/drug use, who participated in a trial of substance use treatment. Participants were assessed for AUD based on DSM-IV criteria. Measures of marijuana use, depression symptoms, and functional status related to mental health were collected at baseline, 3, and 6 months. Differences in these outcomes were analyzed among patients with and without AUD using growth models, adjusting for treatment effects. Marijuana was examined as both an outcome (patterns of use) and a predictor (impact on depression and functioning). Forty percent used marijuana and about half the sample met AUD criteria. Fewer patients with AUD used marijuana than those without AUD at baseline. Over 6 months, the proportion of patients with AUD using marijuana increased compared to those without AUD. Patients with AUD using marijuana had greater depressive symptoms and worse functioning than those without AUD. These findings indicate that marijuana use is clinically problematic for psychiatry outpatients with depression and AUD. Addressing marijuana in the context of psychiatry treatment may help improve outcomes.

Bancks, M. P., R. Auer, et al. (2018). "Self-reported marijuana use over 25 years and abdominal adiposity: the Coronary Artery Risk Development in Young Adults (CARDIA) Study." Addiction **113**(4): 689-698.

AIMS: We investigated the association between cumulative lifetime and current marijuana use with total abdominal adipose tissue (AT), visceral AT, subcutaneous AT, intermuscular AT, and mean liver attenuation (LA) at mid-life. DESIGN: Longitudinal and cross-sectional secondary data analysis of participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. SETTING: CARDIA field centers in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA, USA. PARTICIPANTS: CARDIA participants, aged 18-30 years in 1985-1986, who were present at the clinic examination in 2010-2011 (n = 2902). MEASUREMENTS: Marijuana use was assessed from responses to self-administered questionnaires at 8 CARDIA examinations over 25 years, determined as cumulative marijuana-years and current use status. Non-contrast computed tomography imaging of the abdomen was obtained in 2010-2011. FINDINGS: In 2010-2011, 84% of participants reported a history of marijuana use with 11% reporting use within the past 30 days. Before adjustment, we observed greater cumulative marijuana use was associated with lower total abdominal and subcutaneous AT volume and lower LA and current marijuana use was associated with lower subcutaneous AT. However, after adjustment for age, sex, race, field center, cigarette pack-years and current use, regular alcohol consumption, cumulative drink-years, and physical activity, neither cumulative marijuana use nor current use showed an association with any abdominal adipose depot. Our estimates did not differ by age, sex, or race nor after accounting for cohort attrition. CONCLUSION: Neither cumulative marijuana use nor current marijuana use is associated with total abdominal, visceral, subcutaneous, or intermuscular adipose tissue, or liver attenuation in mid-life.

Barach, E., M. Slavin, et al. (2020). "Cannabis and Vulvodynia Symptoms: A Preliminary Report." Cannabis **3**.

Medical marijuana has a long history of use as an analgesic for chronic pain disorders, including dyspareunia (pain during intercourse), a hallmark of the rare chronic pain disorder vulvodynia. Many women's health topics remain under investigated. Few studies address cannabis's potential to treat vulvodynia symptoms despite their dramatic impact on quality of life. Women who had used cannabis and who reported experiencing vulvodynia symptoms (N = 38) completed an online survey assessing symptoms, expectancies regarding cannabis-associated relief from vulvodynia symptoms, cannabis use, and cannabis-related problems. Generally, women expected cannabis to have moderate to large effects on vulvodynia symptoms (d = .63-1.19). Nevertheless, women expected greater relief for burning/stabbing pain than for itching and pain associated with tampon insertion, as well greater relief for dyspareunia than for pain associated with tampon insertion. Those whose symptoms were worse expected more relief from cannabis treatment. Expectations of cannabis-induced relief did not increase frequency of use or problems. These data support the idea that further work is warranted, including placebo-controlled randomized clinical trials to rule out any placebo effects and identify potential adverse side effects from a cannabis treatment for vulvodynia.

Barbara, A. Y., R. Richard, et al. (2017). "Effect of marijuana use on cardiovascular and cerebrovascular mortality: A study using the National Health and Nutrition Examination Survey linked mortality file." European Journal of Preventive Cardiology **24**(17): 1833-1840.

BackgroundReports associate marijuana use with cardiovascular emergencies. Studies relating marijuana use to cardiovascular mortality are scarce. Recent advance towards marijuana use legalization emphasizes the importance of understanding relationships between marijuana use and cardiovascular deaths; the primary ranked mortality. Recreational marijuana is primarily smoked; we hypothesize that like cigarette smoking, marijuana use will be associated with increased cardiovascular mortalities.DesignThe design of this study was based on a mortality follow-up.MethodWe linked participants aged 20 years and above, who responded to questions on marijuana use during the 2005 US National Health and Nutrition Examination Survey to data from the 2011 public-use linked mortality file of the National Center for Health Statistics, Centers for Disease Control and Prevention. Only participants eligible for mortality follow-up were included. We conducted Cox proportional hazards regression analyses to estimate hazard ratios for hypertension, heart disease, and cerebrovascular mortality due to marijuana use. We controlled for cigarette smoking and other relevant variables.ResultsOf the 1213 eligible participants 72.5% were presumed to be alive. The total follow-up time was 19,569 person-years. Adjusted hazard ratios for death from hypertension among marijuana users compared to non-marijuana users was 3.42 (95% confidence interval: 1.20?9.79) and for each year of marijuana use was 1.04 (95% confidence interval: 1.00?1.07).ConclusionFrom our results, marijuana use may increase the risk for hypertension mortality. Increased duration of marijuana use is associated with increased risk of death from hypertension. Recreational marijuana use potentially has cardiovascular adverse effects which needs further investigation.

Barber, P. A. (2017). Chapter 51 - Cannabis and Stroke A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 486-493.

Abstract It is likely that there is an association between cannabis and ischemic stroke and transient ischemic attack (TIA). There are multiple reports of mainly younger men, with no vascular risk factors other than tobacco and alcohol use, with symptom onset during or soon after cannabis use. This often follows a marked increase in cannabis intake. The strokes are mainly in the posterior circulation possibly reflecting a greater susceptibility to cannabis induced autonomic changes. Population based studies and retrospective audits have also found an association between ischemic stroke and TIA and cannabis. The numbers of patients using cannabis and presenting with stroke has been increasing in recent years and moves toward legalization for medical and recreational reasons will further increase these numbers. However, a causal association between cannabis and ischemic stroke has not been proven. One of the major confounding factors is tobacco, which is often smoked with cannabis. A causal link between cannabis and stroke is plausible, and a number of lines of evidence point to such a link. These include the temporal association between cannabis use and stroke, and recurrent stroke with cannabis reexposure. Cannabis is associated with myocardial infarction and atrial fibrillation. Myocardial infarction and atrial fibrillation both increase the risk of cardiac embolism, which in turn accounts for 20–25% of ischemic strokes. There is also a reversible cerebral cannabis arteriopathy with reversible vasoconstriction syndrome (RCVS), and (possibly) a more prolonged stenosis of cerebral arteries that has been called multifocal arterial stenosis (MIS). In this chapter, the evidence linking stroke and cannabis, and the lines of evidence pointing to a causal link, will be summarized.

Barker, J. (2018). "Review of the public health risks of widespread cannabis use." R I Med J (2013) **101**(3): 22-25.

This article is a review of the public health risks of widespread cannabis use based on a recent review of the literature. The purpose of this article is to help physicians better educate the public about the dangers of widespread cannabis products. [Full article available at <http://rimed.org/rimedicaljournal-2018-04.asp>].

Bar-Lev Schleider, L., R. Mechoulam, et al. (2018). "Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer." European Journal of Internal Medicine **49**: 37-43.

Background Cancer is a major public health problem as the leading cause of death. Palliative treatment aimed to alleviate pain and nausea in patients with advanced disease is a cornerstone of oncology. In 2007, the Israeli Ministry of Health began providing approvals for medical cannabis for the palliation of cancer symptoms. The aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe the safety and efficacy of this therapy. Methods We analyzed the data routinely collected as part of the treatment program of 2970 cancer patients treated with medical cannabis between 2015 and 2017. Results The average age was 59.5 ± 16.3 years, 54.6% women and 26.7% of the patients reported previous experience with cannabis. The most frequent types of cancer were: breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%) with 51.2% being at stage 4. The main symptoms requiring therapy were: sleep problems (78.4%), pain (77.7%, median intensity 8/10), weakness (72.7%), nausea (64.6%) and lack of appetite (48.9%). After six months of follow up, 902 patients (24.9%) died and 682 (18.8%) stopped the treatment. Of the remaining, 1211 (60.6%) responded; 95.9% reported an improvement in their condition, 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition. Conclusions Cannabis as a palliative treatment for cancer patients seems to be well tolerated, effective and safe option to help patients cope with the malignancy related symptoms.

Barnett, J. R., R. A. Grinspoon, et al. (2020). "The efficacy of cannabidiol on renal angiomyolipoma and subependymal giant cell tumor volume in tuberous sclerosis complex." J Clin Neurosci **77**: 85-88.

In patients with tuberous sclerosis complex (TSC) the upregulation of the mechanistic target of rapamycin (mTOR) pathway leads to the development and growth of subependymal giant cell tumors (SGCTs) and renal angiomyolipomas (AMLs). Drugs that inhibit the mTOR pathway, such as sirolimus, can reduce the size of both SGCTs and AMLs. Recent preclinical studies have suggested cannabidiol (CBD) may mediate the mTOR pathway, however, its exact effects are unclear. This study examines the volumes of SGCTs and renal AMLs in patients with TSC during treatment with purified CBD for refractory epilepsy. We retrospectively reviewed the medical records of patients with TSC with radiological evidence of AMLs and SGCTs who were being treated with plant-derived highly purified CBD in oral solution (Epidiolex®, GW Research Ltd) for refractory epilepsy at Massachusetts General Hospital. Patients who had surgical intervention for AMLs or SGCTS, and patients who had been treated with mTOR inhibitors were excluded. The volumes of SGCTs and dominant renal AML were measured before and after CBD initiation using abdominal and brain scans and compared. Patient demographics and CBD doses were collected from medical records. Six out of the seven dominant renal AMLs and three out of the three SGCTs increased in volume during CBD treatment. One AML had a decrease in volume after CBD initiation which was not considered significant. The results suggest that unlike mTOR inhibitors, CBD treatment does not decrease the volume of SGCTs or AMLs in TSC patients.

Baron, E. P., P. Lucas, et al. (2018). "Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort." The Journal of Headache and Pain **19**(1): 37.

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

Baron, E. P. (2018). "Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science." Headache **58**(7): 1139-1186.

BACKGROUND: Comprehensive literature reviews of historical perspectives and evidence supporting cannabis/cannabinoids in the treatment of pain, including migraine and headache, with associated neurobiological mechanisms of pain modulation have been well described. Most of the existing literature reports on the cannabinoids Delta(9) -tetrahydrocannabinol (THC) and cannabidiol (CBD), or cannabis in general. There are many cannabis strains that vary widely in the composition of cannabinoids, terpenes, flavonoids, and other compounds. These components work synergistically to produce wide variations in benefits, side effects, and strain characteristics. Knowledge of the individual medicinal properties of the cannabinoids, terpenes, and flavonoids is necessary to cross-breed strains to obtain optimal standardized synergistic compositions. This will enable targeting individual symptoms and/or diseases, including migraine, headache, and pain. OBJECTIVE: Review the medical literature for the use of cannabis/cannabinoids in the treatment of migraine, headache, facial pain, and other chronic pain syndromes, and for supporting evidence of a potential role in combatting the opioid epidemic. Review the medical literature involving major and minor cannabinoids, primary and secondary terpenes, and flavonoids that underlie the synergistic entourage effects of cannabis. Summarize the individual medicinal benefits of these substances, including analgesic and anti-inflammatory properties. CONCLUSION: There is accumulating evidence for various therapeutic benefits of cannabis/cannabinoids, especially in the treatment of pain, which may also apply to the treatment of migraine and headache. There is also supporting evidence that cannabis may assist in opioid detoxification and weaning, thus making it a potential weapon in battling the opioid epidemic. Cannabis science is a rapidly evolving medical sector and industry with increasingly regulated production standards. Further research is anticipated to optimize breeding of strain-specific synergistic ratios of cannabinoids, terpenes, and other phytochemicals for predictable user effects, characteristics, and improved symptom and disease-targeted therapies.

Behl, D., S. D'Andre, et al. (2020). "Patterns of use of medical cannabis in a community oncology clinic." Journal of Clinical Oncology **38**: e24111-e24111.

e24111 Background: Despite the fact that cannabis is still illegal in some states, two-thirds of all patients with cancer may have used cannabis at some point in their life to alleviate anorexia, nausea, chronic pain, and/or insomnia. Cannabis remains a Schedule 1 drug on the federal list with drugs such as heroin and LSD, which limits the ability to conduct quality clinical trials. This purpose of this study was to assess the prevalence, reasons for use, methods of use, and perceived benefits of medical cannabis in an adult community oncology clinic. Methods: Patients completed a questionnaire when they checked in for their appointment at the outpatient oncology clinic at Sutter Medical Center, Sacramento. Patients who used marijuana were asked questions regarding the mode of ingestion, perceived benefits, types of underlying cancer, and estimated monthly cost. Results: Of the 775 patients who completed the study to date, 129 men (29.3%) and 54 women (70.1%) responded that they used medical cannabis. Approximately 72% were white, 29.3% had breast cancer, and 13% had lung cancer. 39% percent had a diagnosis of metastatic cancer and 44% were undergoing chemotherapy. The most often stated reasons for use were pain (45%), sleep (43%), nausea (38%); and anxiety/mood (38%). Over 50% reported use of oils and tinctures and 44% used edibles. A smaller percentage preferred vaping (26%) or smoking (30%). Topical use was preferred by fewer patients (17%). Over 58% of patients stated they used more than one method. Most patients felt that use of cannabis helped alleviate symptoms. Marked improvement was reported by 40% patients; moderate improvement by another 41%. Only 13% users stated that they noted little to no improvement. The majority of patients (66%) spent $100 or less per month on marijuana whereas 22% spent between $100 and$200 per month. Conclusions: Medical cannabis is used by approximately one-fourth of all patients in an urban community cancer center in Northern California and the majority reported that cannabis provided improvements in symptoms associated with cancer and its treatment. Further research regarding mechanism of actions and associated risks is warranted.

Benson, M. J., S. V. Abelev, et al. (2020). "Attitudes and Knowledge of Australian Gastroenterologists Around the Use of Medicinal Cannabis for Inflammatory Bowel Disease." Crohn's & Colitis 360 **2**(2).

Medicinal cannabis (MC) is being used for symptomatic relief by many patients with inflammatory bowel disease (IBD), often independently of clinical guidance. Such use presents challenges for supporting clinicians. The aim of this study was to determine the current attitudes, knowledge, and experience of gastroenterologists toward patient use of MC for symptom management in IBD. Australian gastroenterologists (n = 70) and trainees (n = 23) completed an anonymous, 30-item questionnaire, probing their knowledge, attitudes, and experience with MC in managing IBD. Survey data were collected between April and August 2019.Thirty-nine percent of survey respondents reported having patients using MC; however, only a minority supported use of MC in IBD (21%) or expressed a desire to prescribe (28%). Only 6% claimed good understanding of current patient access pathways and only 31% felt comfortable discussing MC with their patients. Some respondents (20%) cited adverse side effects as a reason for not wanting to prescribe, with driving impairment (64%) and impacts on the developing brain (56%) cited as significant concerns. Nonetheless, MC was ranked as less hazardous than corticosteroids, immunomodulators, and biologics by most respondents, and many (53%) were encouraging of patient participation in future clinical trials. Specialist support for the use of MC in IBD patients is relatively low, potentially reflecting the lack of experience and knowledge with MC, uncertain evidence for efficacy, and the often-unorthodox nature of current MC use in patients. This situation may change rapidly with increased familiarity, evidence development, and education around MC prescribing. Cannabis is being used for symptom relief by patients with inflammatory bowel diseases, often independently of their doctor’s guidance. After surveying 93 Australian gastroenterologists, we found only a minority supportive of use or wanting the ability to prescribe, despite being supportive of future research.

Ben-Zeev, B. (2020). "Medical Cannabis for Intractable Epilepsy in Childhood: A Review." Rambam Maimonides medical journal **11**(1): e0004.

In recent years, cannabis has been gaining increasing interest in both the medical research and clinical fields, with regard to its therapeutic effects in various disorders. One of the major fields of interest is its role as an anticonvulsant for refractory epilepsy, especially in the pediatric population. This paper presents and discusses the current accumulated knowledge regarding artisanal cannabis and Epidiolex®, a United States Food and Drug Administration (FDA)-approved pure cannabidiol (CBD), in epilepsy management in pediatrics, by reviewing the literature and raising debate regarding further research directions.

Berg, M. V. D., M. John, et al. (2020). "Cannabis-based medicinal products in arthritis, a painful conundrum." N Z Med J **133**(1515): 35-45.

AIMS: The changing medicolegal climate regarding the medicinal use of cannabinoids in New Zealand will increase the likelihood of patients consulting general practitioners (GPs) about these products. Arthritis is a common medical condition for which cannabis-based products are promoted and used; however, doctors' knowledge about the efficacy and safety of these products in the setting of arthritis may be limited. METHODS: We undertook a rapid review of the medical literature on cannabis-based medicinal products in arthritis. RESULTS: Animal studies have identified endocannabinoid pathways in arthritis that are potentially amenable to interventions. One randomised placebo-controlled trial of Sativex® in adults with rheumatoid arthritis has shown some improvements in pain but not in comparison with a standardised pharmacological treatment regimen. Systematic reviews of cannabis-based products in arthritis have determined that there is currently insufficient evidence to recommend cannabis-based medicines for routine clinical use. There were five ongoing registered clinical trials of cannabis-based products in arthritis, the results of which are yet to be reported. CONCLUSIONS: While animal models have identified possible endocannabinoid pathways in arthritis, there is no clear evidence of benefit in humans or comparative efficacy with current treatments. At this stage, there is little evidence to support GPs prescribing cannabis-based medicinal products for arthritis.

Berger, A. A., J. Keefe, et al. (2020). "Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia." Best Practice & Research Clinical Anaesthesiology.

Fibromyalgia is a complex disease process that is as prevalent as it is poorly understood. Research into the pathophysiology is ongoing, and findings will likely assist in identifying new therapeutic options to augment those in existence today that are still insufficient for the care of a large population of patients. Recent evidence describes the use of cannabinoids in the treatment of fibromyalgia. This study provides a systematic, thorough review of the evidence alongside a review of the seminal data regarding the pathophysiology, diagnosis, and current treatment options. Fibromyalgia is characterized by widespread chronic pain, fatigue, and depressive episodes without an organic diagnosis, which may be prevalent in up to 10% of the population and carries a significant cost in healthcare utilization, morbidity, a reduced quality of life, and productivity. It is frequently associated with psychiatric comorbidities. The diagnosis is clinical and usually prolonged, and diagnostic criteria continue to evolve. Some therapies have been previously described, including neuropathic medications, milnacipran, and antidepressants. Despite some level of efficacy, only physical exercise has strong evidence to support it. Cannabis has been used historically to treat different pain conditions since ancient times. Recent advances allowed for the isolation of the active substances in cannabis and the production of cannabinoid products that are nearly devoid of psychoactive influence and provide pain relief and alleviation of other symptoms. Many of these, as well as cannabis itself, are approved for use in chronic pain conditions. Evidence supporting cannabis in chronic pain conditions is plentiful; however, in fibromyalgia, they are mostly limited. Only a handful of randomized trials exists, and their objectivity has been questioned. However, many retrospective trials and patient surveys suggest the significant alleviation of pain, improvement in sleep, and abatement of associated symptoms. Evidence supporting the use of cannabis in chronic pain and specifically in fibromyalgia is being gathered as the use of cannabis increases with current global trends. While the current evidence is still limited, emerging data do suggest a positive effect of cannabis in fibromyalgia. Cannabis use is not without risks, including psychiatric, cognitive, and developmental as well as the risks of addiction. As such, clinical judgment is warranted to weigh these risks and prescribe to patients who are more likely to benefit from this treatment. Further research is required to define appropriate patient selection and treatment regimens.

Berrocoso, E., R. Rey, et al. (2017). Single oral dose of cannabinoid derivate loaded PLGA nanocarriers relieves neuropathic pain for eleven days.

Neuropathic pain, resistant to opiates and other drugs, is a chronic/persistent state with a complex treatment and often poor efficacy. In this scenario, cannabinoids are increasingly regarded as a genuine alternative. In this paper, and in an experimental animal model of neuropathic pain, we studied the efficacy of three kinds of PLGA nanoparticles containing synthetic cannabinoid CB13: (i) plain nanoparticles (PLGA); (ii) particles coated with PEG chains (PLGA+PEG) and (iii) particles possessing hydrophilic surfaces obtained by covalently binding PEG chains (PLGA-PEG). The optimized formulation, CB13-PLGA-PEG, showed high drug loading (13%) and small size (<300nm) with a narrow distribution and controlled surface properties (near-neutral zeta potential and stable PEG corona). Animal nociceptive behavioral studies were conducted by paw pressure and acetone tests. Versus the free CB13, CB13-PLGA-PEG nanoparticles showed a very noticeable analgesic efficacy with the longest sustained pain-relieving effect, lasting up to eleven days after one oral dose.

Bhardwaj, A. K., D. J. Allsop, et al. (2018). "Randomised Controlled Trial (RCT) of cannabinoid replacement therapy (Nabiximols) for the management of treatment-resistant cannabis dependent patients: a study protocol." BMC Psychiatry 18(1): 140.

BACKGROUND: The cannabis extract nabiximols (Sativex(R)) effectively supresses withdrawal symptoms and cravings in treatment resistant cannabis dependent individuals, who have high relapse rates following conventional withdrawal treatments. This study examines the efficacy, safety and cost-effectiveness of longer-term nabiximols treatment for outpatient cannabis dependent patients who have not responded to previous conventional treatment approaches. METHODS/DESIGN: A phase III multi-site outpatient, randomised, double-blinded, placebo controlled parallel design, comparing a 12-week course of nabiximols to placebo, with follow up at 24 weeks after enrolment. Four specialist drug and alcohol outpatient clinics in New South Wales, Australia. One hundred forty-two treatment seeking cannabis dependent adults, with no significant medical, psychiatric or other substance use disorders. Nabiximols is an oromucosal spray prescribed on a flexible dose regimen to a maximum daily dose of 32 sprays; 8 sprays (total 21.6 mg tetrahydrocannabinol (THC) and 20 mg cannabidiol (CBD)) four times a day, or matching placebo, dispensed weekly. All participants will receive six-sessions of individual cognitive behavioural therapy (CBT) and weekly clinical reviews. Primary endpoints are use of non-prescribed cannabis (self-reported cannabis use days, urine toxicology), safety measures (adverse events and abuse liability), and cost effectiveness (incremental cost effectiveness in achieving additional Quality Adjusted Life Years). Secondary outcomes include, improvement in physical and mental health parameters, substance use other than cannabis, cognitive functioning and patient satisfaction measures. DISCUSSION: This is the first outpatient community-based randomised controlled study of nabiximols as an agonist replacement medication for treating cannabis dependence, targeting individuals who have not previously responded to conventional treatment approaches. The study and treatment design is modelled upon an earlier study with this population and more generally on other agonist replacement treatments (e.g. nicotine, opioids). TRIAL REGISTRATION: Australian and New Zealand Clinical Trial Registry: ACTRN12616000103460 (Registered 1st February 2016).

Bjorling, D. W., Z. (2018). Potential of Endocannabinoids to Control Bladder Pain. FRONTIERS IN SYSTEMS NEUROSCIENCE. **12**

Bladder-related pain is one of the most common forms of visceral pain, and visceral pain is among the most common complaints for which patients seek physician consultation. Despite extensive studies of visceral innervation and treatment of visceral pain, opioids remain a mainstay for management of bladder pain. Side effects associated with opioid therapy can profoundly diminish quality of life, and improved options for treatment of bladder pain remain a high priority. Endocannabinoids, primarily anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are endogenously-produced fatty acid ethanolamides with that induce analgesia. Animal experiments have demonstrated that inhibition of enzymes that degrade AEA or 2-AG have the potential to prevent development of visceral and somatic pain. Although experimental results in animal models have been promising, clinical application of this approach has proven difficult. In addition to fatty acid amide hydrolase (FAAH; degrades AEA) and monacylglycerol lipase (MAGL; degrades 2-AG), cyclooxygenase (COX) acts to metabolize endocannabinoids. Another potential limitation of this strategy is that AEA activates pro-nociceptive transient receptor potential vanilloid 1 (TRPV1) channels. Dual inhibitors of FAAH and TRPV1 or FAAH and COX have been synthesized and are currently undergoing preclinical testing for efficacy in providing analgesia. Local inhibition of FAAH or MAGL within the bladder may be viable options to reduce pain associated with cystitis with fewer systemic side effects, but this has not been explored. Further investigation is required before manipulation of the endocannabinoid system can be proven as an efficacious alternative for management of bladder pain.

Black, N., E. Stockings, et al. (2019). "Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis." The Lancet Psychiatry.

BackgroundMedicinal cannabinoids, including medicinal cannabis and pharmaceutical cannabinoids and their synthetic derivatives, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), have been suggested to have a therapeutic role in certain mental disorders. We analysed the available evidence to ascertain the effectiveness and safety of all types of medicinal cannabinoids in treating symptoms of various mental disorders.

Blake, A., B. A. Wan, et al. (2017). "A selective review of medical cannabis in cancer pain management." Annals of Palliative Medicine: S215-S222.

Insufficient management of cancer-associated chronic and neuropathic pain adversely affects patient quality of life. Patients who do not respond well to opioid analgesics, or have severe side effects from the use of traditional analgesics are in need of alternative therapeutic op-tions. Anecdotal evidence suggests that medical cannabis has potential to effectively manage pain in this patient population. This review presents a selection of representative clinical studies, from small pilot studies conducted in 1975, to double-blind placebo-controlled trials conducted in 2014 that evaluated the efficacy of cannabinoid-based therapies containing tetrahydrocannabinol (THC) and cannabidiol (CBD) for reducing cancer-associated pain. A review of literature published on Medline between 1975 and 2017 identified five clinical studies that evaluated the effect of THC or CBD on controlling cancer pain, which have been reviewed and summarised. Five studies that evaluated THC oil capsules, THC:CBD oromucosal spray (nabiximols), or THC oromucosal sprays found some evidence of cancer pain reduction associated with these therapies. A variety of doses ranging from 2.7–43.2 mg/day THC and 0–40 mg/day CBD were administered. Higher doses of THC were correlated with increased pain relief in some studies. One study found that significant pain relief was achieved in doses as low as 2.7–10.8 mg THC in combination with 2.5–10.0 mg CBD, but there was conflicting evidence on whether higher doses provide superior pain relief. Some reported side effects include drowsiness, hypotension, mental clouding, and nausea and vomiting. There is evidence suggesting that medical cannabis reduces chronic or neu-ropathic pain in advanced cancer patients. However, the results of many studies lacked statistical power, in some cases due to limited number of study subjects. Therefore, there is a need for the conduct of further double-blind, placebo-controlled clinical trials with large sample sizes in order to establish the optimal dosage and efficacy of different cannabis-based therapies.

Bleckwenn, M., K. Weckbecker, et al. (2018). "[Beneficial Effect of Medical Cannabis in the Treatment of a Pharmacoresistant Nausea Associated with a Somatoform Disorder in a Patient with Post-Polio Syndrome]." Dtsch Med Wochenschr **143**(5): 344-348.

HISTORY AND CLINICAL FINDINGS: We report a 79-year-old patient with post-polio syndrome (PPS). In the course of this disease, recurrent upper abdominal pain and a therapy-resistant nausea developed without vomiting. In addition, the patient was limited by the combination of muscular weakness, obesity, dietary-treated diabetes and a degenerative spinal cord injury significantly in its mobility and physical capacity. INVESTIGATIONS AND DIAGNOSIS: Despite extensive diagnostics, no somatic cause could be found neither for the nausea nor for the upper abdominal pain. Due to the psychological stress within the scope of the PPS, the development of a somatoform autonomic function disorder of the upper gastrointestinal tract may have occurred. TREATMENT AND COURSE: Even under combination therapy of antiemetic and pain-modulating drugs, no adequate symptom control could be achieved. In the absence of therapy alternatives and increasing psychological strain the patient was prescribed medical cannabis. Under the therapy there was a relief of the nausea symptoms and decreased pain. CONCLUSION: Cannabis is a treatment option for treatment-resistant symptoms as part of a PPS.

Bloomfield, M. A. P., S. F. Green, et al. (2020). "The effects of acute cannabidiol on cerebral blood flow and its relationship to memory: An arterial spin labelling magnetic resonance imaging study." J Psychopharmacol **34**(9): 981-989.

BACKGROUND: Cannabidiol (CBD) is being investigated as a potential treatment for several medical indications, many of which are characterised by altered memory processing. However, the mechanisms underlying these effects are unclear. AIMS: Our primary aim was to investigate how CBD influences cerebral blood flow (CBF) in regions involved in memory processing. Our secondary aim was to determine if the effects of CBD on CBF were associated with differences in working and episodic memory task performance. METHODS: We used a randomised, crossover, double-blind design in which 15 healthy participants were administered 600 mg oral CBD or placebo on separate days. We measured regional CBF at rest using arterial spin labelling 3 h after drug ingestion. We assessed working memory with the digit span (forward, backward) and n-back (0-back, 1-back, 2-back) tasks, and we used a prose recall task (immediate and delayed) to assess episodic memory. RESULTS: CBD increased CBF in the hippocampus (mean (95% confidence intervals) = 15.00 (5.78-24.21) mL/100 g/min, t(14) = 3.489, Cohen's d = 0.75, p = 0.004). There were no differences in memory task performance, but there was a significant correlation whereby greater CBD-induced increases in orbitofrontal CBF were associated with reduced reaction time on the 2-back working memory task ( r= -0.73, p = 0.005). CONCLUSIONS: These findings suggest that CBD increases CBF to key regions involved in memory processing, particularly the hippocampus. These results identify potential mechanisms of CBD for a range of conditions associated with altered memory processing, including Alzheimer's disease, schizophrenia, post-traumatic stress disorder and cannabis-use disorders.

Bobitt, J., H. Kang, et al. (2020). "Use of cannabis and opioids for chronic pain by older adults: Distinguishing clinical and contextual influences." Drug Alcohol Rev.

INTRODUCTION AND AIMS: Chronic pain is one of the most common health-related conditions experienced by Americans over the age of 65. In this study, we examine the intersection between pain, opioids and cannabis use among older adults in Colorado and Illinois and examine how medical needs and other variables associated with a persons' background and attitudes influence choices concerning the use of opioids and cannabis to treat pain. DESIGN AND METHODS: Data were collected via a survey about cannabis and opioids use, and questions related to individual need factors (e.g. pain, quality of life) and contextual factors (e.g. sex, finances, personal attitudes, interaction with physicians) were included in this study. We built a logistic regression model to evaluate factors associated with drug use and a multinomial regression model to understand factors that influence drug choices between cannabis and opioids. RESULTS: A total of 436 individuals completed the survey; 62 used opioids only, 71 cannabis only and 72 used both. When comparing drug users to non-drug users, pain was significantly associated with using cannabis and/or opioids when controlling for other covariates. However, when we compared cannabis users to opioid users, pain was no longer a determining factor. Instead, other contextual factors such as sex, personal beliefs and physician attitudes influenced an individual's choice between cannabis or opioids. DISCUSSION AND CONCLUSIONS: This study showed that contextual factors appear to have more influence on an individual's decision to use cannabis as an alternative to opioids than individual need or characteristics.

Boland, E. G., M. I. Bennett, et al. (2020). "Cannabinoids for adult cancer-related pain: systematic review and meta-analysis." BMJ Supportive &amp; Palliative Care: bmjspcare-2019-002032.

Objectives There is increased interest in cannabinoids for cancer pain management and legislative changes are in progress in many countries. This study aims to determine the beneficial and adverse effects of cannabis/cannabinoids compared with placebo/other active agents for the treatment of cancer-related pain in adults.Methods Systematic review and meta-analysis to identify randomised controlled trials of cannabinoids compared with placebo/other active agents for the treatment of cancer-related pain in adults to determine the effect on pain intensity (primary outcome) and adverse effects, including dropouts. Searches included Embase, MEDLINE, PsycINFO, Web of Science, ClinicalTrials.gov, Cochrane and grey literature. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.Results We identified 2805 unique records, of which six randomised controlled trials were included in this systematic review (n=1460 participants). Five studies were included in the meta-analysis (1442 participants). All had a low risk of bias. There was no difference between cannabinoids and placebo for the difference in the change in average Numeric Rating Scale pain scores (mean difference −0.21 (−0.48 to 0.07, p=0.14)); this remained when only phase III studies were meta-analysed: mean difference −0.02 (−0.21 to 0.16, p=0.80). Cannabinoids had a higher risk of adverse events when compared with placebo, especially somnolence (OR 2.69 (1.54 to 4.71), p<0.001) and dizziness (OR 1.58 (0.99 to 2.51), p=0.05). No treatment-related deaths were reported. Dropouts and mortality rates were high.Conclusions Studies with a low risk of bias showed that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain.Trial registration number CRD42018107662.

Bowen, L. L. and A. L. McRae-Clark (2018). "Therapeutic Benefit of Smoked Cannabis in Randomized Placebo-Controlled Studies." Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy **38**(1): 80-85.

The medicinal use of marijuana has been legalized in 28 states, with a wide range of specificity for approved medical conditions. Even with the emergence of non–combustion-based delivery systems, 90% of marijuana users in 2014 used smoked marijuana. This review summarizes the data available on the use of smoked marijuana for medical purposes. A literature search was performed to retrieve randomized controlled trials exploring the efficacy of smoked cannabis for treatment of a medical condition. Studies with the primary end point listed as the effect of smoked cannabis on a disease-specific characteristic were included. Open-label studies and studies using other administration methods were excluded. Seven studies met these criteria and were included in this review. Cannabis did not outperform placebo on experimentally evoked pain or the timed walk test. Clear evidence indicates that smoked cannabis reduces intraocular pressure, but the effect is too brief (less than 4 hrs) to be of therapeutic benefit for this chronic disorder. Consistent evidence also showed that smoked marijuana, even at lower concentrations of tetrahydrocannabinol, increased total daily calorie intake and number of eating occasions. Neither of the studies with quality of life as secondary outcome measures revealed statistically significantly improved outcomes with cannabis use.

Bradford, A. C., W. Bradford, et al. (2018). "Association between us state medical cannabis laws and opioid prescribing in the medicare part d population." JAMA Internal Medicine **178**(5): 667-672.

Importance  Opioid-related mortality increased by 15.6% from 2014 to 2015 and increased almost 320% between 2000 and 2015. Recent research finds that the use of all pain medications (opioid and nonopioid collectively) decreases in Medicare Part D and Medicaid populations when states approve medical cannabis laws (MCLs). The association between MCLs and opioid prescriptions is not well understood.Objective  To examine the association between prescribing patterns for opioids in Medicare Part D and the implementation of state MCLs.Design, Setting, and Participants  Longitudinal analysis of the daily doses of opioids filled in Medicare Part D for all opioids as a group and for categories of opioids by state and state-level MCLs from 2010 through 2015. Separate models were estimated first for whether the state had implemented any MCL and second for whether a state had implemented either a dispensary-based or a home cultivation only–based MCL.Main Outcomes and Measures  The primary outcome measure was the total number of daily opioid doses prescribed (in millions) in each US state for all opioids. The secondary analysis examined the association between MCLs separately by opioid class.Results  From 2010 to 2015 there were 23.08 million daily doses of any opioid dispensed per year in the average state under Medicare Part D. Multiple regression analysis results found that patients filled fewer daily doses of any opioid in states with an MCL. The associations between MCLs and any opioid prescribing were statistically significant when we took the type of MCL into account: states with active dispensaries saw 3.742 million fewer daily doses filled (95% CI, −6.289 to −1.194); states with home cultivation only MCLs saw 1.792 million fewer filled daily doses (95% CI, −3.532 to −0.052). Results varied by type of opioid, with statistically significant estimated negative associations observed for hydrocodone and morphine. Hydrocodone use decreased by 2.320 million daily doses (or 17.4%) filled with dispensary-based MCLs (95% CI, −3.782 to −0.859; P = .002) and decreased by 1.256 million daily doses (or 9.4%) filled with home-cultivation–only-based MCLs (95% CI, −2.319 to −0.193; P = .02). Morphine use decreased by 0.361 million daily doses (or 20.7%) filled with dispensary-based MCLs (95% CI, −0.718 to −0.005; P = .047).Conclusions and Relevance  Medical cannabis laws are associated with significant reductions in opioid prescribing in the Medicare Part D population. This finding was particularly strong in states that permit dispensaries, and for reductions in hydrocodone and morphine prescriptions.

Braithwaite, I., C. Bhagavan, et al. (2021). "Medicinal applications of cannabis/cannabinoids." Current Opinion in Psychology **38**: 1-10.

Regulatory approvals for Epidiolex (purified cannabidiol) in the treatment of childhood drug resistant epilepsy have set a precedent for the use of cannabinoids as a prescribed medicine. Two common reasons cited for the use and prescription of cannabis-based products are pain and insomnia. Unlike drug resistant epilepsy, the level of evidence of efficacy in pain is poorly developed. The lowest quality trials with the greatest methodological shortcomings suggest some benefit, a level of evidence that is inconsistent with widespread prescribing. The evidence in insomnia is scant. Ongoing trial development and critical review of the literature should not be overshadowed by increasing permissiveness towards cannabis use and anecdotal reports of efficacy.

Braun, I. M., A. Wright, et al. (2018). "Medical Oncologists' Beliefs, Practices, and Knowledge Regarding Marijuana Used Therapeutically: A Nationally Representative Survey Study." J Clin Oncol **36**(19): 1957-1962.

Background Although almost every state medical marijuana (MM) law identifies cancer as a qualifying condition, little research supports MM's use in oncology. We hypothesized that the discrepancy between these laws and the scientific evidence base poses clinical challenges for oncologists. Oncologists' beliefs, knowledge, and practices regarding MM were examined in this study. Methods In November 2016, we mailed a survey on MM to a nationally-representative, random sample of 400 medical oncologists. Main outcome measures included whether oncologists reported discussing MM with patients, recommended MM clinically in the past year, or felt sufficiently informed to make such recommendations. The survey also queried oncologists' views on MM's comparative effectiveness for several conditions (including its use as an adjunct to standard pain management strategies) and its risks compared with prescription opioids. Bivariate and multivariate analyses were performed using standard statistical techniques. Results The overall response rate was 63%. Whereas only 30% of oncologists felt sufficiently informed to make recommendations regarding MM, 80% conducted discussions about MM with patients, and 46% recommended MM clinically. Sixty-seven percent viewed it as a helpful adjunct to standard pain management strategies, and 65% thought MM is equally or more effective than standard treatments for anorexia and cachexia. Conclusion Our findings identify a concerning discrepancy between oncologists' self-reported knowledge base and their beliefs and practices regarding MM. Although 70% of oncologists do not feel equipped to make clinical recommendations regarding MM, the vast majority conduct discussions with patients about MM and nearly one-half do, in fact, recommend it clinically. A majority believes MM is useful for certain indications. These findings are clinically important and suggest critical gaps in research, medical education, and policy regarding MM.

Brigden, M. and D. England (2018). Medical marijuana and community oncology practice: the good, the bad, and the potentially ugly. **17**:10-17.

Apart from immuno-oncology agents, few topics in the past two years have generated more questions for medical oncologists, and attention from the popular press, than medical marijuana. While a great deal is known about the various medicinal cannabinoids, in oncology large gaps persist relating to basic pharmacology and potential drug interactions. The situation is further complicated by the lack of randomized controlled clinical trials and the huge variety of cannabinoid preparations and formulations currently available, each presenting biochemical complexity and quality control issues. This lack of high-level scientific evidence, coupled with deficiencies in pertinent physician education, ethical issues, and complex federal and provincial college regulations, leave many clinicians in the dark on how to advise individual patients. This review provides a practical update in relation to many of these concerns, as well as summarizing the current state of regulation and prescribing of medical marijuana in Canada.

Brill, J. B., R. J. Schutt, et al. "Cannabis and Other Substance Use in Solid Organ Transplant Patients." Journal of the American College of Surgeons **225**(4): e167-e168.

Recent legislation in 7 states prohibits denial of transplantation solely on the basis of cannabis use. Evidence is lacking regarding the impact of cannabis use on transplant recipients, with case reports comprising the majority of available literature. To address this need, we investigated cannabis use, known risk factors for poor outcomes, and self-reported outcomes in our center's recipients.

Briscoe, J. and D. Casarett (2018). "Medical Marijuana Use in Older Adults." J Am Geriatr Soc **66**(5):

859-863.

Symptom management in older adults, including pain and distressing non-pain symptoms, can be challenging. Medications can cause side effects that worsen quality of life or create other symptoms, and polypharmacy itself can be detrimental in older adults. Cannabinoids may offer a way of managing selected symptoms with fewer side effects. Medical marijuana is an important area of study for older adults because of the side effects of other medications. It is also important for Baby Boomers, who are likely to have more experience with marijuana than older adults of previous generations. Therefore, geriatricians should understand medical marijuana's clinical indications, adverse effects, and legal context. This article reviews the evidence regarding indications for and risks of medical marijuana use in older adults.

Brodie, M. J. and E. Ben-Menachem (2018). "Cannabinoids for epilepsy: What do we know and where do we go?" Epilepsia **59**(2): 291-296.

Over the past decade there has been an increasing interest in using cannabinoids to treat a range of epilepsy syndromes following reports of some remarkable responses in individual patients. The situation is complicated by the fact that these agents do not appear to work via their attachment to endogenous cannabinoid receptors. Their pharmacokinetics are complex, and bioavailability is variable, resulting in difficulty in developing a suitable formulation for oral delivery. Drug interactions also represent another complication in their everyday use. Nevertheless, recent randomized, placebo-controlled trials with cannabidiol support its efficacy in Dravet and Lennox-Gastaut syndromes. Further placebo-controlled studies are underway in adults with focal epilepsy using cannabidivarin. The many unanswered questions in the use of cannabinoids to treat epileptic seizures are briefly summarized in the conclusion.

Brown, J. D. and A. G. Winterstein (2019). "Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use." J Clin Med 8(7).

Cannabidiol (CBD) is ubiquitous in state-based medical cannabis programs and consumer products for complementary health or recreational use. CBD has intrinsic pharmacologic effects and associated adverse drug events (ADEs) along with the potential for pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs). Given CBD use among patients with complex conditions and treatment regimens, as well as its expanded consumer use, awareness of potential safety issues with CBD is needed. Prescribing information for federally approved products containing CBD were reviewed. Data on ADEs and DDIs were extracted and summarized. Nearly one-half of CBD users experienced ADEs, which displayed a general dose-response relationship. Common ADEs include transaminase elevations, sedation, sleep disturbances, infection, and anemia. Given CBD effects on common biological targets implicated in drug metabolism (e.g., CYP3A4/2C19) and excretion (e.g., P-glycoprotein), the potential for DDIs with commonly used medication is high. General clinical recommendations of reducing substrate doses, monitoring for ADEs, and finding alternative therapy should be considered, especially in medically complex patients. CBD is implicated as both a victim and perpetrator of DDIs and has its own ADE profile. These effects should be considered in the risk-benefit assessment of CBD therapy and patients and consumers made aware of potential safety issues with CBD use.

Brown, M. R. D. and W. P. Farquhar-Smith (2018). "Cannabinoids and cancer pain: A new hope or a false dawn?" European Journal of Internal Medicine **49**: 30-36.

The endocannabinoid system is involved in many areas of physiological function and homeostasis. Cannabinoid receptors are expressed in the peripheral and central nervous system and on immune cells, all areas ideally suited to modulation of pain processing. There are a wealth of preclinical data in a number of acute, chronic, neuropathic and cancer pain models that have demonstrated a potent analgesic potential for cannabinoids, especially in patients with cancer. However, although there are some positive results in pain of cancer patients, the clinical evidence for cannabinoids as analgesics has not been convincing and their use can only be weakly recommended. The efficacy of cannabinoids seems to have been ‘lost in translation’ which may in part be related to using extracts of herbal cannabis rather than targeted selective full agonists at the cannabinoid CB1 and CB2 receptors.

Bruce, D., J. P. Brady, et al. (2017). "Preferences for Medical Marijuana over Prescription Medications Among Persons Living with Chronic Conditions: Alternative, Complementary, and Tapering Uses." The Journal of Alternative and Complementary Medicine **24**(2): 146-153.

Abstract Objectives: Despite expanded legalization and utilization of medical cannabis (MC) internationally, there is a lack of patient-centered data on how MC is used by persons living with chronic conditions in tandem with or instead of prescription medications. This study describes approaches to use of MC vis-à-vis prescription medications in the treatment of selected chronic conditions. Design: Participants completed semistructured telephone interviews with open-ended questions. Content analysis of qualitative data identified themes and subthemes relating to patient approaches to using MC products. Participants: Thirty persons (mean age?=?44.6 years) living with a range of chronic conditions (e.g., rheumatoid arthritis, Crohn's disease, spinal cord injury/disease, and cancer) who had qualified for and used MC in Illinois. Results: Participants described a range of approaches to using MC, including (1) as alternatives to using prescription or over-the-counter medications; (2) complementary use with prescription medications; and (3) as a means for tapering off prescription medications. Motives reported for reducing or eliminating prescription medications included concerns regarding toxicity, dependence, and tolerance, and perceptions that MC improves management of certain symptoms and has quicker action and longer lasting effects. Conclusions: MC appears to serve as both a complementary method for symptom management and treatment of medication side-effects associated with certain chronic conditions, and as an alternative method for treatment of pain, seizures, and inflammation in this population. Additional patient-centered research is needed to identify specific dosing patterns of MC products associated with symptom alleviation and produce longitudinal data assessing chronic disease outcomes with MC use.   
Objectives: Despite expanded legalization and utilization of medical cannabis (MC) internationally, there is a lack of patient-centered data on how MC is used by persons living with chronic conditions in tandem with or instead of prescription medications. This study describes approaches to use of MC vis-à-vis prescription medications in the treatment of selected chronic conditions. Design: Participants completed semistructured telephone interviews with open-ended questions. Content analysis of qualitative data identified themes and subthemes relating to patient approaches to using MC products. Participants: Thirty persons (mean age?=?44.6 years) living with a range of chronic conditions (e.g., rheumatoid arthritis, Crohn's disease, spinal cord injury/disease, and cancer) who had qualified for and used MC in Illinois. Results: Participants described a range of approaches to using MC, including (1) as alternatives to using prescription or over-the-counter medications; (2) complementary use with prescription medications; and (3) as a means for tapering off prescription medications. Motives reported for reducing or eliminating prescription medications included concerns regarding toxicity, dependence, and tolerance, and perceptions that MC improves management of certain symptoms and has quicker action and longer lasting effects. Conclusions: MC appears to serve as both a complementary method for symptom management and treatment of medication side-effects associated with certain chronic conditions, and as an alternative method for treatment of pain, seizures, and inflammation in this population. Additional patient-centered research is needed to identify specific dosing patterns of MC products associated with symptom alleviation and produce longitudinal data assessing chronic disease outcomes with MC use.

Brown University (2020) "Insufficient evidence for cannabinoids in the treatment of mental disorders." The Brown University Psychopharmacology Update **31**(2): 1-6.

The most comprehensive review to date of medicinal cannabinoids for the treatment of mental disorders has concluded that the evidence is insufficient to justify their use. A greater number of high-quality trials is necessary to assess the safety and efficacy of medical cannabis and derivatives such as the increasingly popular cannabidiol (CBD), authors of the review and meta-analysis stated. Results were published online Oct. 28 in Lancet Psychiatry.

Buchanan-Peart, K.-A. R., G. I. Oribhabor, et al. (2020). "Cannabis, More Than the Euphoria: Its Therapeutic Use in Drug-Resistant Epilepsy." Cureus **12**(7): e9299-e9299.

A significant number of epilepsy patients are refractory to conventional antiepileptic drugs. These patients experience considerable neurocognitive impairments that impact their quality of life and ability to function independently. This need for alternative treatment has generated increased interest in cannabis use as a therapeutic option in these patients. This review seeks to analyze data presented on the pharmacology, safety, and efficacy of cannabis use in patients with drug-resistant epilepsy (DRE) and to propose any future recommendations regarding its use. PubMed was used to retrieve all published studies and articles which evaluated the use of cannabis in epilepsy. The two foremost phytocannabinoids of cannabis showing anticonvulsant properties are tetrahydrocannabinol (THC) and cannabidiol (CBD). Due to the psychoactive properties of THC, most studies focused on CBD use in these patients. The use of CBD as an adjunct resulted in decreased seizure frequency, and secondary benefits observed included improvement in mood, alertness and sleep. Adverse events (AEs) reported were drowsiness, diarrhea, increased transaminases and worsening of seizures. It can safely be concluded that there is a significant benefit in DRE patients using CBD as adjunctive therapy. However, further controlled and adequately powered studies are needed to assess the pharmacokinetics and impact of the long-term use of cannabis.

Buchwald, D., D. Brønnum, et al. (2020). "Living with a Hope of Survival Is Challenged by a Lack of Clinical Evidence: An Interview Study among Cancer Patients Using Cannabis-Based Medicine." J Palliat Med **23**(8): 1090-1093.

Background: There is an increasing focus among cancer patients on the use of cannabis-based medicine (CBM) as a supplement to conventional palliative care. However, physicians are reluctant to engage in dialog with the patients as clinical evidence is lacking. As a result, the patients are often left alone to rely on their own judgment in purchasing CBM products on the illegal market. Objective: Our study aimed to collect information from CBM treatment-experienced cancer patients receiving palliative care regarding treatment decision rationale and outcome. Design: A qualitative interview study using thematic analysis was performed. Setting/Participants: A total of 20 informants took part in individual interviews. Results: To the question addressing the main rationale for starting CBM treatment, all 20 patients responded that they carried a hope that cannabis would have a curative effect on the cancer disease. Most patients reported relief of symptoms, such as insomnia, anxiety, nausea, and pain, after initiation of CBM treatment, but this outcome was perceived as less of a focus in comparison to hope of a cure. Conclusion: This study contributes with knowledge from the perspective of the cancer patient in palliative care regarding the decision behind the use of CBM. There seems to be striving for surviving cancer based on the rationale that cannabis may constitute curative properties. Relief of symptoms is perceived as a secondary reason for treatment. This knowledge is essential in the dialog between the health professional and the cancer patient about the use of CBM products for treatment.

Calabrò, R. S., M. Russo, et al. (2020). "Nabiximols plus robotic assisted gait training in improving motor performances in people with Multiple Sclerosis." Multiple Sclerosis and Related Disorders **43**: 102177.

Background Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, affecting ambulation even in people with only mild neurological signs. Patients with MS frequently experience spasticity, which contributes significantly to impair their motor functions, including ambulation, owing to muscle stiffness, spasms, and pain. Objectives To clarify the role of delta-9-tetrahydrocannabinol(THC):cannabidiol(CBD) oromucosal spray, coupled to robot-aided gait training (RAGT) using the Lokomat©Pro to improve functional ambulation in patients with MS. Methods We compared 20 patients with MS, who were treated with THC:CBD oromucosal spray in add-on to the ongoing oral antispastic therapy (OAT) (group A), with 20 individuals with MS (matched for clinical-demographic characteristics) who were treated only with OAT (group B). Both the groups underwent RAGT using the Lokomat-Pro (three 45-minute sessions per week). Our primary outcome measures were the Functional Independence Measure (FIM) and the 10 meters walking test (10MWT). As secondary outcome measures we evaluated the brain cortical excitability by using Transcranial Magnetic Stimulation. Both parameters were taken before and after the end of the RAGT. Results FIM improved in group A more than in group B (p<0.001). Moreover, 10MWT decreased in group A more than in group B (p<0.001). These clinical findings were paralleled by a more evident reshape of intracortical excitability in both upper and lower limbs, as suggested by motor evoked potential amplitude increase (p<0.001), intracortical inhibition strengthening (p<0.001), and intracortical facilitation decrease (p=0.01) in group A as compared to group B. Conclusions Our results suggest that the combined THC:CBD-RAGT approach could be useful in improving gait performance in patients with MS.

Calapai, G., C. Mannucci, et al. (2019). "Preclinical and Clinical Evidence Supporting Use of Cannabidiol in Psychiatry." Evidence-Based Complementary and Alternative Medicine 2019: 11.

Background. Cannabidiol (CBD) is a major chemical compound present in Cannabis sativa. CBD is a nonpsychotomimetic substance, and it is considered one of the most promising candidates for the treatment of psychiatric disorders. Objective. &e aim of this review is to illustrate the state of art about scientific research and the evidence of effectiveness of CBD in psychiatric patients. Methods. &is review collects the main scientific findings on the potential role of CBD in the psychiatric field, and results of clinical trials carried out on psychiatric patients are commented. A research was conducted in the PUBMED, SCOPUS, and ScienceDirect databases using combinations of the words cannabidiol, psychiatry, and neuropsychiatric. Results. Preclinical and clinical studies on potential role of CBD in psychiatry were collected and further discussed. We found four clinical studies describing the effects of CBD in psychiatric patients: two studies about schizophrenic patients and the other two studies carried out on CBD effects in patients affected by generalized social anxiety disorder (SAD). Conclusion. Results from these studies are promising and suggest that CBD may have a role in the development of new therapeutic strategies in mental diseases, and they justify an in-depth commitment in this field. However, clinical evidence we show for CBD in psychiatric patients is instead still poor and limited to schizophrenia and anxiety, and it needs to be implemented with further studies carried out on psychiatric patients.

Callaghan, R. C., P. Allebeck, et al. (2017). "Cannabis use and incidence of testicular cancer: a 42-year follow-up of Swedish men between 1970 and 2011." Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology **26**(11): 1644-1652.

BACKGROUND: Given current drug-policy reforms to decriminalize or legalize cannabis in numerous countries worldwide, it is critically important to understand the potential impacts of cannabis use on the development of cancer. The current study aims to assess the relation between cannabis use and the development of testicular cancer. METHOD: The current study relied on a population-based sample (n = 49 343) of young men aged 18–21 years who underwent conscription assessment for Swedish military service in 1969–1970. The conscription process included a non-anonymous questionnaire eliciting information about drug use. Individual-level conscription information was linked to Swedish health and social registry data. Testicular cancers diagnosed between 1970 and 2011 were identified by ICD-7/8/9/10 testicular cancer codes in the Swedish National Patient Register, the Cancer Register, or the Cause of Death Register. Cox regression modeling was used to estimate the hazards associated with cannabis use and time to diagnosis of testicular cancer. RESULTS: No evidence was found of a significant relation between lifetime “ever” cannabis use and the subsequent development of testicular cancer [n = 45 250; 119 testicular cancer cases; adjusted hazard ratio (AHR) 1.42, 95% CI, 0.83, 2.45]. “Heavy” cannabis use (defined as usage of more than 50 times in lifetime, as measured at conscription) was associated with the incidence of testicular cancer (n = 45 250; 119 testicular cancer cases; AHR 2.57, 95% CI, 1.02, 6.50). CONCLUSION: The current study provides additional evidence to the limited prior literature suggesting cannabis use may contribute to the development of testicular cancer.

Callaghan, R. C., M. Verdichevski, et al. (2017). Chapter e9 - Does Cannabis Use Increase the Risk of Developing Cancer in Humans? A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** e80-e100.

Abstract Given that many countries worldwide are currently debating or implementing the decriminalization or legalization of marijuana use, it is critically important for policymakers and the public to have scientific information about the potential impacts of marijuana use on human health. Marijuana and tobacco smoke both contain powerful carcinogens and, so, we conducted a narrative review of all relevant scientific evidence published over the last decade (2004–14) to answer the following question: “Does marijuana use increase the risk of developing cancer in humans?” There were 19 studies identified as eligible for assessment. Of the seven studies on lung cancer, five found that marijuana use significantly increased the risk of lung cancer, but the two best-designed studies (which used stratification across tobacco-use status) found no evidence of increased risk. The strong possibility of residual confounding by tobacco use, especially in studies finding increased lung cancer risk, undermines any definitive interpretation of the results. Across six studies, four papers demonstrated no evidence of a significantly increased risk of head and neck cancers associated with marijuana use. Few studies on head and neck cancer or lung cancer, however, included sufficient numbers of long-term marijuana users with substantial joint-years of usage (eg, &gt;10 joint-years) and, as a result, a possible association between chronic, heavy marijuana use and these cancer outcomes cannot be ruled out. Three studies showed a potential relation between marijuana use and increased risk of nonseminoma testicular cancers. For the field to advance, researchers need to make strong efforts to include the following in their studies: detailed marijuana exposure assessments; information about primary route of marijuana administration; strict account of tobacco smoking, the best being through stratification across tobacco-use history; sufficiently large samples of chronic or heavy marijuana users (eg, individuals with &gt;10 joint-years of exposure); and, where possible, pooled analyses or meta-analytic approaches.

Calcaterra, S. L., A. N. Burnett-Hartman, et al. (2020). "A population-based survey to assess the association between cannabis and quality of life among colorectal cancer survivors." BMC Cancer **20**(1): 373.

As more states legalize cannabis for medical and recreational use, people increasingly use cannabis to treat medical conditions and associated symptoms. The prevalence and utility of cannabis for cancer-related symptoms may be clarified by examining cannabis use among patients with a common cancer diagnosis. We aimed to determine the prevalence of cannabis use among colorectal cancer (CRC) survivors and its associations with quality of life (QoL) and cancer-related symptomatology.

Calcaterra, S. L., C. O. Cunningham, et al. (2020). "The Void in Clinician Counseling of Cannabis Use." J Gen Intern Med **35**(6): 1875-1878.

As more states legalize cannabis for medical use, people increasingly use cannabis to treat medical conditions. Well-documented harms of cannabis use include increased risk of fatal auto accidents, neurocognitive deficits, and increased risk of addiction. Observational data supports the use of cannabis for pain, nausea and vomiting related to chemotherapy, and multiple sclerosis spasticity symptoms. Given potential harms versus benefits of cannabis use, how should physicians counsel patients regarding their cannabis use? This paper briefly reviews the evidence supporting medical cannabis use for pain. We consider cannabis use as a harm reduction strategy for pain management. We encourage routine, longitudinal assessments of cannabis use among patients. We discuss the commercialization of cannabis for financial gain, contributing to potent and addictive cannabis. We highlight the concerning phenomena of cannabis dispensary workers as proxy clinicians. Finally, we present three strategies to reduce public harms associated with potent cannabis use including required testing and reporting of tetrahydrocannabinol/cannabidiol concentrations, rigorous study of high-potency cannabis available for purchase in dispensaries across the USA, and large-scale efforts to measure cannabis consumption in medical records so prospective, longitudinal studies can be conducted to correlate consumption measures with medical and psychiatric outcomes.

Cameron, E. and S. Hemingway (2020). "Cannabinoids for Fibromyalgia Pain: A Critical Review of Recent Studies (2015-2019) Journal of Cannabis Research."

Introduction: Fibromyalgia is a chronic health condition characterized by widespread, severe musculoskeletal pain that affects an estimated 5-7% of the global population. Due to the highly comorbid nature of fibromyalgia, patients with the disorder often respond poorly to traditional pain treatments. Recent studies suggest that patient response may be more favorable to alternative analgesics, such as cannabis. However, the therapeutic potential of cannabis-based pain treatment for fibromyalgia remains unclear. The present study examined the most recent cannabis literature (2015-2019) and provides a critical review of current research on the safety and efficacy of medical cannabis treatments for fibromyalgia. Methods: We followed Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines in searching the PubMed and Medline databases using the search terms “cannabis + fibromyalgia” and then “cannabinoids + fibromyalgia.” Inclusion criteria were a) English language, b) published in peer review journals, c) published from 2015 to 2019, d) all study designs except for systematic reviews and meta-analyses, and e) all cannabis preparations. Results: The search identified five applicable studies involving 827 participants that used six different treatments. Review suggested several methodological problems pertaining to generalizability and validity. Conclusion: Although the critically reviewed studies superficially suggest that medical cannabis is a safe and effective treatment for fibromyalgia pain, serious methodological limitations prevent a definitive conclusion regarding the use of cannabinoids for pain management in fibromyalgia patients at this time.

Campbell, G., W. D. Hall, et al. (2018). "Effect of cannabis use in people with chronic non-cancer pain

prescribed opioids: findings from a 4-year prospective cohort study." The Lancet Public Health 3(7):

e341-e350.

Background: Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioids paring effects of cannabis.

Cao, R., J. Wang, et al. (2017). Is Marijuana Beneficial for Prevention and Treatment of Diabetes?

Marijuana is classified as Cannabis saiva L, one type of hemp. Traditionally, Marijuana is considered as Schedule I drug due to its acute bad effects on human health. However, its medical use has been widely recognized today. Delta-9-tetrahydrocannabinol ( 9-THC) is a compound extracted from Marijuana, which has been used in several drugs approved by United States Food and Drug Administration (FDA).  9-THC functions through cannabinoid receptor in neural system or peripheral tissues. For diabetes patients,  9-THC has been reported to have preventative or treatment effects. In this paper, we will review recent research progress in association between cannabis use and diabetes, as well as known mechanism of how  9-THC functions in human from the perspective of free radicals.

Capra, S., S. W. Narayan, et al. (2020). "Cannabinoids for drug-resistant seizures in a critically ill patient-Case report and literature review." J Clin Pharm Ther **45**(3): 570-572.

WHAT IS KNOWN AND OBJECTIVE: Drug-resistant seizures are life-threatening and contribute to sustained hospitalization. We present the case of a critically ill 28-year-old male with Lennox-Gastaut syndrome who had approximately 30 seizures/day in the intensive care unit. CASE DESCRIPTION: Patient required mechanical ventilation and pharmacologically induced thiopentone coma. He was commenced on cannabidiol and subsequently extubated. He remained seizure-free thereafter on a combination of cannabidiol and anti-epileptic medication that predated his critical illness. WHAT IS NEW AND CONCLUSION: Our case report provides a unique perspective on the role of cannabidiol in achieving remission from drug-resistant seizures in critically ill patients.

Cassano, T., R. Villani, et al. (2020). "From Cannabis sativa to Cannabidiol: Promising Therapeutic Candidate for the Treatment of Neurodegenerative Diseases." Front Pharmacol **11**: 124.

Cannabis sativa, commonly known as marijuana, contains a pool of secondary plant metabolites with therapeutic effects. Besides Delta9-tetrahydrocannabinol that is the principal psychoactive constituent of Cannabis, cannabidiol (CBD) is the most abundant nonpsychoactive phytocannabinoid and may represent a prototype for anti-inflammatory drug development for human pathologies where both the inflammation and oxidative stress (OS) play an important role to their etiology and progression. To this regard, Alzheimer's disease (AD), Parkinson's disease (PD), the most common neurodegenerative disorders, are characterized by extensive oxidative damage to different biological substrates that can cause cell death by different pathways. Most cases of neurodegenerative diseases have a complex etiology with a variety of factors contributing to the progression of the neurodegenerative processes; therefore, promising treatment strategies should simultaneously target multiple substrates in order to stop and/or slow down the neurodegeneration. In this context, CBD, which interacts with the eCB system, but has also cannabinoid receptor-independent mechanism, might be a good candidate as a prototype for anti-oxidant drug development for the major neurodegenerative disorders, such as PD and AD. This review summarizes the multiple molecular pathways that underlie the positive effects of CBD, which may have a considerable impact on the progression of the major neurodegenerative disorders.

Castañeda, J. (2020). "User perspectives on cannabis and SSRIs as treatment for depression." Drugs and Alcohol Today **ahead-of-print**.

Purpose The purpose of this paper is to explore the qualitative relationship between cannabis and the most commonly used antidepressant drugs known as selective serotonin reuptake inhibitor (SSRIs) through the narratives of depressed individuals who have used both drugs at one point during their lifetime. Despite their prevalence, depression, cannabis use, and SSRI use have not been previously studied together through the perspective of those who have experienced them. Using a exploratory approach, this paper investigates and compares the user experiences of these drugs. Design/methodology/approach Semi-structured interviews were conducted involving participants who were between the ages of 16–59 in the UK and have used both SSRIs and cannabis either simultaneously or at any point in their lives. Five interviews were conducted either via telephone or in person, and the method of analysis was an inductive approach which was inspired by grounded-theory. Findings While the two drugs were used by participants in order to relieve symptoms of depression, they were used for very different reasons and typically at different stages of their lives. Though participants did not state that the drugs were interchangeable for improving mood, their responses indicated that these drugs were viewed as two alternatives to alleviate symptoms of depression. Participants’ relationships with their doctors also played a crucial role and affected interviewees’ decisions to use either SSRIs or cannabis, as well as perceptions of the medical industry. Social implications This research shows the importance of doctor and patient interactions as they were crucial influences on patients’ decisions related to drugs. Participants’ experiences with SSRI and cannabis were subjective and varied, therefore, the value of personalised treatment (which may or may not include psychotropic drugs) is highlighted. These findings can help health practitioners gain a better understanding of the rationale of depressed patients in choosing treatments and thereby improve healthcare outcomes. Originality/value Given that depression is stigmatised, and cannabis use is both illegal and stigmatised, this paper examines the opinions of a difficult to reach population. Previous work involving cannabis, antidepressants and mood-elevating effects is primarily written with a biochemical or medical perspective which paid more focus on the efficacy of these drugs and had less emphasis on the beliefs of the users. This paper highlights the opinions of cannabis and SSRI users regarding these two drugs specifically, which had not been previously explored.

Cawich, S. O., U. Deonarine, et al. (2017). Chapter 46 - Cannabis and Postoperative Analgesia A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 450-458.

Abstract Despite detailed knowledge of nociceptive mechanisms, postoperative pain continues to be inadequately managed worldwide. Although morphine remains the drug of choice to treat moderate and severe postoperative pain, its unfavorable side effects have sparked interest in adjuvant therapies. A better understanding of the endocannabinoid system has raised a potential role for cannabinoids in the treatment of postoperative pain. Animal trials and some clinical studies have reported on the use of cannabis and cannabinoids in the postoperative period, with mixed results. There is mounting experimental evidence to suggest that there is synergism between opioids and cannabinoids enhancing analgesia. On the other hand, there are reports suggesting increased postoperative analgesia requirements in chronic cannabis users. We examine the use of cannabis in the treatment of postoperative pain, synergism between opioids and cannabinoids, and the postoperative analgesic requirements of the chronic cannabis user.

Celius Elisabeth, G. and C. Vila (2018). "The influence of THC:CBD oromucosal spray on driving ability in patients with multiple sclerosis‐related spasticity." Brain and Behavior **8**(5): e00962.

Abstract Background Driving ability is a key function for the majority of patients with multiple sclerosis (MS) to help maintain daily interactions. Both physical and cognitive disability, as well as treatments, may affect the ability to drive. Spasticity is a common symptom associated with MS, and it may affect driving performance either directly or via the medications used to treat it. In this article, we review the evidence relating the antispasticity medicine, ?9?tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (Sativex?), and its potential impact on driving performance. Methods Articles were identified by searching PubMed from 1/1/2000 to 30/6/2017 using a specified list of search terms. The articles identified using these search terms were augmented with relevant references from these papers and other articles known to the authors. Results The results from THC:CBD oromucosal spray driving studies and real?world registries did not show any evidence of an increase in motor vehicle accidents associated with THC:CBD oromucosal spray. The majority of patients reported an improvement in driving ability after starting THC:CBD oromucosal spray, and it was speculated that this may be related to reduced spasticity and/or better cognitive function. It should be noted that THC blood levels are significantly lower than the levels associated with recreational use of herbal cannabis. Conclusions THC:CBD oromucosal spray was shown not to impair driving performance. However, periodic assessment of patients with MS driving ability is recommended, especially after relapses and changes in treatment. Blood THC measurements might be above authorized thresholds for some countries following administration of THC:CBD oromucosal spray, thus specific knowledge of each country's driving regulations and a medical certificate are recommended.

Chang, Y. D., J. S. Smith, et al. (2017). "Cannabis use in palliative care: The prevalence and clinical characteristics." Journal of Clinical Oncology **35**(31\_suppl): 245-245.

Background: Cannabis has growing attention in palliative care, been used for some cancer related symptom burden, but limited data in terms of prevalence in palliative care setting and clinical characteristics with using it. Purpose: To identify the prevalence of positive rate of cannabis metabolite on urine drug sample (UDS) and compare clinical characteristics focused on symptoms burden on Edmonton Symptom Assessment Scale (ESAS) on the same day of UDS. Methods: We conducted retrospective medical records review of 919 consecutive supportive care clinic patients who were seen at a National Cancer Institute center during a 12-month period between 7/01/2015 to 6/30/2016. Results: 531 out of 919 patients were excluded because UDS was not ordered: either patients were established or had low risk of substance abuse by clinicians’ judgement. 2 patients did not complete ESAS on same day of UDS. 137 patients were excluded because of missing UDS results as well. Finally, 249 out of 919 patients were included for data analysis with their UDS and ESAS at same day of visit. 54 patients were positive for cannabis metabolite (THC: tetrahydrocannabinol) on UDS (22%). We found that positive cannabis group was younger (Mean age 56.1 vs 48.8, p-Value .001), reported higher score of total ESAS (Mean 45.5 vs 38.9, p-value 0.023), pain (Mean 6.13 vs 4.99, p-Value 0.007), and insomnia (6.04 vs 4.44, p-Value 0.001). In addition, positive cannabis group reported poorer overall wellbeing (5.43 vs 4.56, p-Value 0.015) and spiritual wellbeing (6.04 vs 4.44, p Value 0.040) compared to negative cannabis group. Conclusions: The positive results of cannabis on UDS may be a marker of greater symptom burden, in particular, pain, insomnia and poorer overall and spiritual wellbeing as assessed by ESAS patient’s self-reporting.

Chao, Y. S. and S. McCormack (2019). Medicinal and Synthetic Cannabinoids for Pediatric Patients: A Review of Clinical Effectiveness and Guidelines. Medicinal and Synthetic Cannabinoids for Pediatric Patients: A Review of Clinical Effectiveness and Guidelines. Ottawa (ON), Canadian Agency for Drugs and Technologies in Health

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Cannabinoids are pharmacologically active agents extracted from the cannabis plant.(1) Cannabidiol and tetrahydrocannabinol (THC) are the most studied cannabinoids and both interact with endocannabinoid receptors in various human tissues.(1) The endocannabinoid system moderates physiological functions, such as neurodevelopment, cognition, and motor control.(2) The products naturally derived from cannabis include marijuana (dried leaves and flowers, mostly for smoking) and oral cannabinoid extracts with varying concentrations of cannabinoids, including cannabidiol and THC.(1) THC is the main psychoactive constituent and cannabidiol seems to have no psychoactive properties.(2) In addition, there are two synthetical cannabinoids approved by the Food and Drug Administration (FDA) in the United States, dronabinol and nabilone, which are molecules similar to a type of THC (delta-9-THC)(1) Nabilone is also approved in Canada.(3) Dronabinol is indicated for chemotherapy-induced nausea and vomiting in children.(1) The use of nabilone in children is not recommended.(1) In Canada, the minimum age for cannabis consumption varies by provinces and territories, and is either 18 or 19 years.(4) A prescription is required to administer cannabinoids among children.(4) Clinically, cannabis has been used to treat children with epilepsy,(5) cancer palliation and primary treatment, chronic pain, and Parkinson disease.(6) The adverse events that clinicians need to monitor for include negative psychoactive sequelae and development of tolerance.(6) Psychoactive sequelae may be positive, such as relaxation and euphoria, or negative, such as anxiety and irritability.(2) In 2016, CADTH completed a Summary of Abstracts report on the use of cannabis in children with medical conditions such as attention deficit hyperactivity disorder, autism spectrum disorder, Tourette syndrome, epilepsy, posttraumatic stress disorder, or neurodegenerative diseases, and five non-randomized studies were identified.(7) However, there were no control groups in the five studies included in the report.(8)(-)(12) It is unclear whether there is new evidence or clinical guidance for the use of medical cannabis in children with mental health conditions, neurodegenerative diseases, or pain disorders, particularly in comparison with other possible therapies for those conditions. There is a need to review the clinical effectiveness of cannabis for pediatric care, as well as clinical guidelines.

Chen KA, F. M., Cardamone M, Gill D, Smith R, Cowell CT, Truong L, Lawson JA (2018). "Cannabidiol for treating drug-resistant epilepsy in children: the New South Wales experience." Med J Aust **209**(5): 217-221.

Objective: To evaluate the tolerability and safety of cannabidiol for treating drug-resistant epilepsy in children, and to describe adverse events associated with such treatment.

Study design: Prospective, open label cohort study.

Setting: Three tertiary NSW referral centres with paediatric neurology services.

Participants: First 40 children enrolled in the NSW Compassionate Access Scheme for children with drug-resistant epilepsy and uncountable daily seizures.

Intervention: Children received cannabidiol as an adjunct anti-epileptic drug, titrated to a maximum of 25 mg/kg/day, for up to 12 weeks.

Outcome measures: Adverse events, withdrawals, and caregiver and physician Global Impression of Change assessments were recorded at 4, 8 and 12 weeks. Seizure frequency could not be reliably recorded because of disease severity.

Results: Thirty-nine patients reported at least one adverse event; many were deemed unrelated to cannabidiol treatment. The most frequent treatment-related adverse event was somnolence (15 participants), which resolved spontaneously in ten patients; it was particularly frequent in patients taking higher clobazam doses. Gastrointestinal effects (nausea, vomiting, diarrhoea) were each reported by seven to nine participants. Four children were withdrawn from treatment, including one with elevated transaminase levels. The caregivers of 12 children felt the overall health of their children had much or very much improved; clinicians assessed seven children as being much or very much improved.

Conclusion: Cannabidiol as an adjunct treatment had some subjective benefit for overall health, with a manageable adverse event profile. Monitoring changes in liver function and awareness of potential drug interactions is essential. Whether the reported benefit is attributable to cannabidiol cannot be established in an open label study of participants with severe intractable epilepsy.

Chisari, C., P. Annunziata, et al. (2020). "Nabiximols discontinuation rate in a large population of patients with multiple sclerosis: a 18-month multicentre study." Journal of Neurology, Neurosurgery & Psychiatry: jnnp-2019.

Introduction Delta-δ-tetrahydrocannabinol and cannabidiol (THC:CBD) oromucosal spray is used as an add-on therapy option for moderate to severe multiple sclerosis (MS) spasticity resistant to other medications. Aims of this study were to provide real-life data on long-term clinical outcomes in a large population of Italian patients treated with THC:CBD and to evaluate predictors of THC:CBD therapy continuation. Materials and methods This prospective observational multicentre Italian study screened all patients with MS consecutively included in the Agenzia Italiana del Farmaco e-registry at the start of THC:CBD treatment (baseline), after 4 weeks (T1), 12±3 weeks (T2), 24±3 weeks (T3), 48±3 weeks (T4) and 72±3 weeks (T5) from baseline. Results A total of 1845 patients were recruited from 32 MS Italian centres. At T1, 1502 (81.4%) of patients reached a Numerical Rating Scale (NRS) improvement of ≥20%, with an NRS reduction of 26.9% at T1 and of 34.4% at T5. At T5, 725 patients (48.3% of 1502) discontinued treatment with highest discontinuation rate at T2 and T3. Daily number of puffs was generally stable through the observation period. The multivariate analysis showed that higher NRS scores at baseline (OR 2.28, 95% CI 1.15 to 6.36, p<0.01) and higher differences of NRS between T0 and T1 (OR 2.11, 95% CI 1.08 to 8.26, p<0.05) were associated with an increased probability to continue therapy after 18 months. Discussion THC:CBD effects were sustained for 18 months with a relatively stable number of puffs per day. About 50% of patients abandoned THC:CBD therapy for loss of efficacy or adverse events.

Chiurchiù, V., M. van der Stelt, et al. (2018). "The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: Clues for other neuroinflammatory diseases." Progress in Neurobiology **160**: 82-100.

Multiple sclerosis is the most common inflammatory demyelinating disease of the central nervous system, caused by an autoimmune response against myelin that eventually leads to progressive neurodegeneration and disability. Although the knowledge on its underlying neurobiological mechanisms has considerably improved, there is a still unmet need for new treatment options, especially for the progressive forms of the disease. Both preclinical and clinical data suggest that cannabinoids, derived from the Cannabis sativa plant, may be used to control symptoms such as spasticity and chronic pain, whereas only preclinical data indicate that these compounds and their endogenous counterparts, i.e. the endocannabinoids, may also exert neuroprotective effects and slow down disease progression. Here, we review the preclinical and clinical studies that could explain the therapeutic action of cannabinoid-based medicines, as well as the medical potential of modulating endocannabinoid signaling in multiple sclerosis, with a link to other neuroinflammatory disorders that share common hallmarks and pathogenetic features.

Choi, S., B. C. Huang, et al. (2020). "Therapeutic Uses of Cannabis on Sleep Disorders and Related Conditions." Journal of Clinical Neurophysiology **37**(1): 39-49.

Summary: Marijuana generally refers to the dried mixture of leaves and flowers of the cannabis plant, and the term cannabis is a commonly used to refer to products derived from the Cannabis sativa L. plant. There has been an increasing interest in the potential medicinal use of cannabis to treat a variety of diseases and conditions. This review will provide the latest evidence regarding the medical risks and potential therapeutic benefits of cannabis in managing patients with sleep disorders or those with other medical conditions who commonly suffer with sleep disturbance as an associated comorbidity. Published data regarding the effects of cannabis compounds on sleep in the general population, as well as in patients with insomnia, chronic pain, posttraumatic stress disorder, and other neurological conditions, will be presented. Current trends for marijuana use and its effects on the economy and the implications that those trends and effects have on future research into medical cannabis are also presented.

Chye, Y., E. Christensen, et al. (2019). "The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder." Front Psychiatry 10: 63.

Substance use disorder is characterized by repeated use of a substance, leading to clinically significant distress, making it a serious public health concern. The endocannabinoid system plays an important role in common neurobiological processes underlying substance use disorder, in particular by mediating the rewarding and motivational effects of substances and substance-related cues. In turn, a number of cannabinoid drugs (e.g., rimonabant, nabiximols) have been suggested for potential pharmacological treatment for substance dependence. Recently, cannabidiol (CBD), a non-psychoactive phytocannabinoid found in the cannabis plant, has also been proposed as a potentially effective treatment for the management of substance use disorder. Animal and human studies suggest that these cannabinoids have the potential to reduce craving and relapse in abstinent substance users, by impairing reconsolidation of drug-reward memory, salience of drug cues, and inhibiting the reward-facilitating effect of drugs. Such functions likely arise through the targeting of the endocannabinoid and serotonergic systems, although the exact mechanism is yet to be elucidated. This article seeks to review the role of the endocannabinoid system in substance use disorder and the proposed pharmacological action supporting cannabinoid drugs' therapeutic potential in addictions, with a focus on CBD. Subsequently, this article will evaluate the underlying evidence for CBD as a potential treatment for substance use disorder, across a range of substances including nicotine, alcohol, psychostimulants, opioids, and cannabis. While early research supports CBD's promise, further investigation and validation of CBD's efficacy, across preclinical and clinical trials will be necessary.

Clarke, S., L. Vitetta, et al. (2020). An oro-buccal nanoparticle delivered cannabis medicine for pain management in cancer: A clinical trial in progress.

TPS12127 Background: Cannabinoid molecules derived from Cannabis sativa L. have been posited to ameliorate conditions, including pain, chemotherapy induced nausea and multiple sclerosis associated spasticity. The clinical use of cannabinoids refers to a wide variety of formulations and extracts that may contain different active ingredients and adulterants as well as inter batch variability. Novel matrix formulations (e.g., water-soluble nanoparticles) for cannabis delivery may add further efficacy and tolerability to standard routes of administration (e.g., oral / gastrointestinal, inhaled, sublingual). This is further emphasized by the dysbiotic effects on the intestinal microbiome reported for oral formulations of medicinal cannabis, and which resulted in reduced efficacy. Similar results have been reported for other psychotropic compounds, such as alcohol and nicotine. Therapeutic use of cannabinoid formulations may be mode of delivery dependent in order to achieve safe, tolerable and effective doses. Methods: A water soluble oro-buccal nanoparticle spray with a racemic 1:1 mixture of Delta9Tetrahydrocannabinol (D9THC) and Cannabidiol (CBD), which bypasses the gastrointestinal system and first pass metabolism by accessing the systemic circulation via the facial lymphatics system, was investigated in patients with advanced cancer and unrelieved pain in a single ascending dose and multiple ascending dose in a first-in-human study. Results: The THC / CBD combination delivered as a submicron particle demonstrated safety, tolerability and a pharmacokinetic profile suitable for maintenance analgesic therapy. Preliminary analysis found an overall (n = 25) improvement in pain scores, especially in the subgroup of patients with bone metastases (n = 8), who obtained a greater than 30% average reduction in pain severity. 1 Clinical trial information: ACTRN12617001480370 .

Cohen, K. and A. M. Weinstein (2018). "Synthetic and Non-synthetic Cannabinoid Drugs and Their

Adverse Effects-A Review From Public Health Prospective." Front Public Health 6: 162.

There is a growing use of novel psychoactive substances containing synthetic cannabinoids. Synthetic cannabinoid products have effects similar to those of natural cannabis, yet, these drugs are more potent and dangerous, and have been associated with dangerous adverse effects. Here, we review current literature on the epidemiology, acute, and chronic effects of synthetic and natural cannabinoid-based drugs. Synthetic drugs contain a mixture of psychoactive compounds that mostly bind cannabinoid receptors with high potency. These synthetic drugs replicate the effects of natural cannabis and Delta9-tetrahydrocannabinol but they induce more severe adverse effects including respiratory difficulties, hypertension, tachycardia, chest pain, muscle twitches, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment. Chronic use of synthetic cannabinoids has been associated with serious psychiatric and medical conditions and even death. Given the growing popularity in the use of cannabinoid-based drugs and their harmful potential, there is a need for further research in this field.

Colwill, A. C., K. Alton, et al. (2020). "Cannabinoids for Pain Control During Medical Abortion: A Randomized Controlled Trial." Obstetrics & Gynecology **135**(6).

OBJECTIVE: To evaluate whether prophylactic dronabinol, a synthetic tetrahydrocannabinol, reduces pain during medical abortion. METHODS: We conducted a randomized, double-blind, placebo-controlled trial of women undergoing medical abortion with mifepristone and misoprostol up through 70 days of gestation. All participants received 800 mg of ibuprofen and were randomized to either 5 mg of oral dronabinol or a placebo 30 minutes before misoprostol administration. Participants used a text messaging service to report pain on a numeric rating scale from 0 to 10 (0=no pain, 10=worst pain). The primary outcome was maximum pain experienced during the 24 hours after misoprostol administration. Secondary outcomes were pain scores at 0, 6, and 24 hours after misoprostol administration; maximum anxiety and nausea scores; use of additional pain medication; reported side effects; and satisfaction (yes or no). We needed 68 participants (34 per group) to have 80% power to detect a 2-point difference in maximum pain on a numeric rating scale. RESULTS: From November 2018 to May 2019, we randomized 70 women (dronabinol=35, placebo=35). Participants in the study arms had comparable baseline characteristics. We found no difference between groups in the median maximum pain score reported (dronabinol 7 [interquartile range 6–8], placebo 7 [interquartile range 5–8], P=.82) or median pain scores at any timepoint. Groups were also no different in mean maximum anxiety (dronabinol 3.33 [SD 3.06], placebo 3.23 [SD 2.53], P=.88) or nausea scores (dronabinol 2.21 [SD 2.32], placebo 2.72 [SD 2.64], P=.41). Most women were satisfied with their pain management (76% dronabinol, 82% placebo, P=.51). CONCLUSION: Dronabinol does not reduce the maximum level of pain experienced by women undergoing medical abortion. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT03604341.

Cooke, A., L. Chavez, et al. (2020). "The relationships between chronic pain and changes in health with cannabis consumption patterns." Int J Drug Policy **76**: 102657.

BACKGROUND: Pain is the most common reason endorsed by patients seeking medical cannabis. Given the nature of chronic pain, it is particularly important to understand consumption patterns for patients who use cannabis for chronic health conditions to evaluate how frequency of use might impact overall health and functioning. This analysis examines whether levels of chronic pain were associated with cannabis consumption patterns, after controlling for patient-level differences in demographics. METHODS: Our sample included 295 medical cannabis patients. Logistic regression models were fit to evaluate the association between pain (low, moderate and high) and dichotomous measures of cannabis consumption (daily vs. nondaily; ≥3 times per day vs. <3 times per day). Additionally, two ordered logit models were fit to evaluate the association between past-year health status change (better, same, or worse) and cannabis consumption. RESULTS: A significantly higher proportion of respondents in the high pain category used cannabis 3 or more times per day, compared to lower pain categories. Pain level was not significantly associated with daily cannabis use. However, pain level was significantly associated with log odds of using cannabis ≥3 times per day, such that respondents with both high pain and moderate pain had significantly higher log odds of consuming cannabis ≥3 times per day compared to low pain group. CONCLUSION: While the efficacy of cannabis for various medical conditions continues to be evaluated, the best available evidence suggests a possible benefit for the treatment of chronic pain. The results of this study indicate that individuals with high pain are more likely to consume cannabis multiple times a day, but this use may not be related to better health. Our results point to a need for more research on the health impacts of frequency of cannabis use among medical cannabis dispensary patients.

Cook, A. C., G. Leung, et al. (2020). "Marijuana Decriminalization, Medical Marijuana Laws, and Fatal Traffic Crashes in US Cities, 2010–2017." American Journal of Public Health **110**(3): 363-369.

Objectives. To determine the impact of city-level cannabis decriminalization and medical marijuana laws (MMLs) on fatal traffic crashes in US cities.Methods. Using a census of fatal traffic crashes from the 2010 to 2017 Fatality Analysis Reporting System, we examined MMLs and cannabis decriminalization on fatal crashes by age and sex of driver. We used a Poisson difference-in-differences approach, exploiting temporal and geographic variation in marijuana decriminalization laws.Results. Cities experienced a 13% increase in fatal crashes involving 15- to 24-year-old male drivers following decriminalization (incidence rate ratio = 1.125; 95% confidence interval = 1.014, 1.249). This effect was immediate and strongest on weekend nights. We found no effect on female drivers or older males. Conversely, we found that MMLs were associated with fewer fatal crashes for both males and females, which was most pronounced in 15- to 24-year-old drivers.Conclusions. Unlike MMLs, which are associated with fewer fatal crashes, cities experienced a relative increase in fatal crashes involving young male drivers following marijuana decriminalization.Public Health Implications. MMLs stipulate consumption occurs at home, whereas decriminalization only lessens the penalty for marijuana possession. Therefore, travel incentives of such laws have heterogeneous effects on traffic safety.

Cooke, A. C., K. R. Knight, et al. (2019). "Patients' and clinicians' perspectives of co-use of cannabis and opioids for chronic non-cancer pain management in primary care." Int J Drug Policy **63**: 23-28.

BACKGROUND: The prevalence of opioid-associated morbidity and mortality underscores the need for research on non-opioid treatments for chronic non-cancer pain (CNCP). Pain is the most common medical condition for which patients request medical cannabis. Limited research indicates that patients are interested in cannabis as a potential addition to or replacement for opioid medication. This analysis reports on CNCP patient and clinician perceptions about the co-use of cannabis and opioids for CNCP management. METHODS: We interviewed 23 clinicians and 46 CNCP patients, using semi-structured interview guides, from six safety-net clinics across the San Francisco Bay Area, and 5 key stakeholders involved in CNCP management. We used a modified grounded theory approach to code and analyze transcripts. RESULTS: CNCP patients described potential benefits of co-use of cannabis and opioids for pain management and concerns about dosing and addictive potential. Patients reported seeking cannabis when unable to obtain prescription opioids. Clinicians stated that their patients reported cannabis being helpful in managing pain symptoms. Clinicians expressed concerns about the potential exacerbation of mental health issues resulting from cannabis use. CONCLUSION: Clinicians are hampered by a lack of clinically relevant information about cannabis use, efficacy and side-effects. Currently no guidelines exist for clinicians to address opioid and cannabis co-use, or to discuss the risk and benefits of cannabis for CNCP management, including side effects. Cannabis and opioid co-use was commonly reported by patients in our sample, yet rarely addressed during clinical CNCP care. Further research is needed on the risks and benefits of cannabis and opioid co-use.

Cooke, A., L. Chavez, et al. (2020). "The relationships between chronic pain and changes in health with cannabis consumption patterns." Int J Drug Policy **76**: 102657.

BACKGROUND: Pain is the most common reason endorsed by patients seeking medical cannabis. Given the nature of chronic pain, it is particularly important to understand consumption patterns for patients who use cannabis for chronic health conditions to evaluate how frequency of use might impact overall health and functioning. This analysis examines whether levels of chronic pain were associated with cannabis consumption patterns, after controlling for patient-level differences in demographics. METHODS: Our sample included 295 medical cannabis patients. Logistic regression models were fit to evaluate the association between pain (low, moderate and high) and dichotomous measures of cannabis consumption (daily vs. nondaily; >/=3 times per day vs. <3 times per day). Additionally, two ordered logit models were fit to evaluate the association between past-year health status change (better, same, or worse) and cannabis consumption. RESULTS: A significantly higher proportion of respondents in the high pain category used cannabis 3 or more times per day, compared to lower pain categories. Pain level was not significantly associated with daily cannabis use. However, pain level was significantly associated with log odds of using cannabis >/=3 times per day, such that respondents with both high pain and moderate pain had significantly higher log odds of consuming cannabis >/=3 times per day compared to low pain group. CONCLUSION: While the efficacy of cannabis for various medical conditions continues to be evaluated, the best available evidence suggests a possible benefit for the treatment of chronic pain. The results of this study indicate that individuals with high pain are more likely to consume cannabis multiple times a day, but this use may not be related to better health. Our results point to a need for more research on the health impacts of frequency of cannabis use among medical cannabis dispensary patients.

Cosker, E., T. Schwitzer, et al. (2018). "The effect of interactions between genetics and cannabis use on neurocognition. A review." Progress in Neuro-Psychopharmacology and Biological Psychiatry **82**: 95-106.

Background Cannabis is one of the most widely-used drugs in industrialized countries. It is now well established that cannabis use impacts neurocognition. In the intoxication period time episodic memory, working memory and attention are impacted and impulsivity is increased. The long-term effects of cannabis use tend to be similar. Various internal factors, such as sex differences, modulate this impact. It is unclear whether genetic variations can also influence the impact of cannabis on neurocognition. We set out to examine the impact of genetic variations on neurocognition in cannabis users. Method We conducted a search via the PubMed, Web of Science, and ScienceDirect databases to identify studies measuring neurocognition and assessing genotypes in the context of cannabis use. Results We included 13 articles. We found that working memory, verbal and visual memory and sustained attention are more impacted during intoxication in subjects with the Val COMT allele. COMT gene could also modulate sustained attention in regular use. The CNR1, AKT1, DBH and 5-HTT/SLC6A4 genes may also modulate effects. Conclusion Most of these genes are linked to schizophrenia. A fuller understanding of their impact on the effects of cannabis on neurocognition would thus help elucidate the mechanisms linking cannabis and psychosis. However, evidence is still scant, and more research is needed.

Coskun, Z. M. and S. Bolkent (2017). Chapter 80 - The Role of Δ9-Tetrahydrocannabinol in Diabetes Mellitus A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 779-786.

Abstract Diabetes mellitus is characterized by hyperglycemia. However, dyslipidemia, oxidative stress, and inflammation are major risks in the development of diabetes and its complications. Δ9-Tetrahydrocannabinol (Δ9-THC) is the main constituent of Cannabis sativa. Δ9-THC is known as a natural phytocannabinoid and agonist of cannabinoid receptors. The cannabinoid 1 and cannabinoid 2 receptors (CB1 and CB2) are included in the endocannabinoid system. Recent studies have provided evidence that expressions and functions of cannabinoid receptors exist in the islets of Langerhans. Furthermore, according to studies, both the agonist and antagonist of cannabinoid receptors influence the regulation of food intake and energy homeostasis. Δ9-THC, a cannabinoid receptor agonist, may play a role on the effects of reactive oxygen species production, inflammation, insulin secretion, and lipids regulation. This review focused on the role of Δ9-THC in diabetes.

Couch, D. G., C. Tasker, et al. (2017). "Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon." Clin Sci (Lond) **131**(21): 2611-2626.

OBJECTIVE: We sought to quantify the anti-inflammatory effects of two cannabinoid drugs, cannabidiol (CBD) and palmitoylethanolamide (PEA), in cultured cell lines and compared this effect with experimentally inflamed explant human colonic tissue. These effects were explored in acutely and chronically inflamed colon, using inflammatory bowel disease and appendicitis explants. DESIGN: Caco-2 cells and human colonic explants collected from elective bowel cancer, inflammatory bowel disease (IBD) or acute appendicitis resections, and were treated with the following drug treatments: vehicle, an inflammatory protocol of interferon gamma (IFNgamma) and tumour necrosis factor alpha (TNFalpha; 10 ng/ml), inflammation and PEA (10 microM), inflammation and CBD (10 microM), and PEA or CBD alone, CBD or vehicle were added simultaneously with IFNgamma. Nine intracellular signalling phosphoproteins were determined by multiplex. Inflammatory cytokine secretion was determined using ELISA. Receptor mechanisms were investigated using antagonists for CB1, CB2, PPARalpha, PPARgamma, TRPV1 and GPR55. RESULTS: IFNgamma and TNFalpha treatment increased phosphoprotein and cytokine levels in Caco-2 cultures and colonic explants. Phosphoprotein levels were significantly reduced by PEA or CBD in Caco-2 cultures and colonic explants. CBD and PEA prevented increases in cytokine production in explant colon, but not in Caco-2 cells. CBD effects were blocked by the CB2 antagonist AM630 and TRPV1 antagonist SB366791. PEA effects were blocked by the PPARalpha antagonist GW6471. PEA and CBD were anti-inflammatory in IBD and appendicitis explants. CONCLUSION: PEA and CBD are anti-inflammatory in the human colon. This effect is not seen in cultured epithelial cells. Appropriately sized clinical trials should assess their efficacy.

Coyne, z., D. Cowzer, et al. (2020). "Cannabis and cancer: Examining the use and perceived benefits in an Irish cancer cohort." Journal of Clinical Oncology **38**: e24178-e24178.

e24178 Background: Medicinal cannabis is currently approved for symptom control in cancer patients. There is limited evidence to suggest cannabis is efficacious in the treatment of cancer. In this study we aim to characterise the extent of cannabis use in patients receiving anti-cancer therapies and what impact they think cannabis use has on their cancer. Methods: An anonymous survey was distributed to patients with cancer attending the Beaumont Hospital Oncology Day Unit for anti-cancer therapy over a period of 4 weeks. Results: 175 patients completed the survey. 166 (95%) of patients said they would be comfortable talking to their oncologist about cannabis use. 161 (92%) felt their oncologist should prescribe cannabis as part of their cancer treatment. 17% thought cannabis would cure their cancer. 38% thought cannabis would slow the growth of their cancer and 33% thought cannabis would treat cancer related symptoms. 42 (24%) of all patients had tried some form of cannabis at least once in their life. 26 (15%) were actively taking CBD (Cannabidiol) oil as part of their treatment independently of any healthcare professional guidance. More females (15) were taking CBD compared to males (11). A higher proportion of patients < 50 years (14) were taking CBD during their treatment. 30% of patients using CBD had breast cancer and 23% had a primary CNS malignancy. Of the patients taking CBD, 20 (77%) patients felt it would cure or slow cancer growth and 10 (38%) patients believed it would help with cancer related symptoms. Conclusions: Patients with cancer appear to have a positive attitude towards cannabis as part of their treatment despite limited evidence to support this. With the increasing availability of cannabis-based products globally, medical oncologists must now take into consideration patient’s attitude towards cannabis while treating their cancer

Cranford, J. A., J. T. Arnedt, et al. (2017). "Prevalence and correlates of sleep-related problems in adults receiving medical cannabis for chronic pain." Drug and alcohol dependence **180**: 227-233.

To examine the prevalence and correlates of sleep problems in a sample of medical cannabis patients.Adults ages 21 and older (N=801,M age=45.8) who were seeking medical cannabis certification (either for the first time or as a renewal) for chronic pain at medical cannabis clinics in southern Michigan completed baseline measures of cannabis use, sleep, pain, and other related constructs.Over half of the sample (59%) met criteria for past 1-month sleep disturbance, defined as at least one sleep problem occurring on 15 or more nights in the past month. Most participants (86%) reported that sleep problems were due to their current pain. Approximately 80% of participants reported using cannabis in the past 6 months to improve sleep and, among these participants, cannabis was rated as helpful for improving sleep. Sleep-related cannabis side effects were rare (35%), but sleep-related cannabis withdrawal symptoms were relatively common (65%). Statistically significant correlates of past 1-month sleep disturbance included a) being female, b) being white, c) being on disability, d) not having a medical cannabis card, and e) frequency of using cannabis to help sleep.Sleep problems are highly prevalent and frequent in medical cannabis patients and are closely tied to pain. Sleep-related cannabis withdrawal symptoms are relatively common but their clinical relevance is unknown. The association between frequency of cannabis use to help sleep with higher odds of sleep problems will need to be clarified by longitudinal studies.

Creedon, E. S., M. K. Maloy, et al. (2019). "Cannabinoid hyperemesis syndrome: A case study and discussion." Journal of the American Association of Nurse Practitioners Online Now.

Background and purpose: Cannabinoid hyperemesis syndrome (CHS) was first described in the literature in 2004. The pathophysiology of CHS remains largely unknown. The syndrome is becoming more prevalent in inpatient settings and emergency departments as the legal usage of cannabis proliferates, although it is often not recognized when encountered. While symptoms of CHS are becoming better defined, early recognition and comprehensive treatment plans with reproducible outcomes remain elusive. Symptoms can be further complicated by the presence of chronic conditions or comorbidities. The purpose of this article is to consolidate findings from the literature, identify commonalities in clinical characteristics and pathogenesis, and highlight diagnostic and treatment approaches. Methods: Data collection methods include a review of the literature on CHS published in the past 10 years. Case study data were gathered from a patient interview and chart review. Conclusions and implications for practice: Through better recognition of CHS, nurse practitioners and other providers can promptly and accurately diagnosis the condition and improve treatment plans for these patients. Correspondence: Eliza S. Creedon, BSN, MBA, RN, Student AGACNP, 4110 Porosa Lane, Prosper, TX. Tel: (917) 886-4283; Fax: (972) 920-3290; E-mail: ecreedon@twu.edu Competing interests: The authors report no conflicts of interest. Authors'contributions: E. Creedon and M. Maloy are equal contributors in the development, analysis, and writing of the case study in its entirety. R. DelloStritto served as a mentor, editor, and content reviewer. Received December 18, 2018 Received in revised form February 01, 2019 Accepted February 11, 2019 © 2019 American Association of Nurse Practitioners

Croker Iii, J. A., J. L. Bobitt, et al. (2020). "Assessing Health-Related Outcomes of Medical Cannabis Use among Older Persons: Findings from Colorado and Illinois." Clin Gerontol: 1-14.

OBJECTIVES: To assess health-related outcomes associated with medical cannabis use among older patients in Colorado and Illinois enrolled in their home state's medical cannabis program. METHODS: Cross-sectional data from anonymous surveys were collected from 139 persons over the age of 60 using medical cannabis in the past year. We used structural equation modeling (SEM) to confirm the hypothesized four-factor structure that includes health-related quality of life (HRQL), health-care utilization (HCU), symptom effects, and adverse events. We then examined associations between cannabis use and self-reported outcome changes using linear regression. RESULTS: The four-factor model was the best fitting structure (X2(df) = 81.63 (67), p> X2 = 0.108) relative to reduced structures. We also found that using cannabis 1-4 times per week is associated with 3.30 additional points on the HRQL scale (p < .001), 2.72 additional points on the HCU scale (p < .01), and 1.13 points on pain (p < .001). The frequency of use reported at 5-7 times per week is associated with 4.71 additional HRQL score points (p < .001). No significant associations were observed between the frequency of use and adverse events. CONCLUSIONS: We observed how cannabis use outcomes fall into four independent factors, and those using more frequently reported higher values on HRQL, HCU, and pain measures. However, we are cautious about the generalizability of our findings. CLINICAL IMPLICATIONS: Clinicians should consider how older patients using medical cannabis can experience positive and negative outcomes simultaneously or separately and assess these outcomes directly along with considering patient self-reports.

Crowell, T. L. (2017). "Therapeutic Value of Medical Marijuana in New Jersey Patients: A Community Partnership Research Endeavor." J Allied Health **46**(4): 232-238.

OBJECTIVE: The Public Health Program at Stockton University partnered with the Compassionate Care Foundation to ascertain the impact of medical marijuana on patients in New Jersey. METHODS: Patients volunteered to complete a survey once a month for 8 months. The survey explored their use, form, and strain of medical marijuana and its influence on pain and 12 other physical and mental health variables. Also, an increase or decrease in other medication taken and any unexpected outcomes were recorded. RESULTS: From a total of 955 patients, patients responding to the surveys varied from 501 for visit 1, 290 for visit 2, to 179 for visit 3. Results provide insight into the diagnoses for which patients used medical marijuana. Results indicate increased mood, general overall condition, and energy as the highest consequences; level of pain in the middle range; and most frequent usage as 3 to 4 times a day. Repeated measures done after visit 2 showed eight statistically significant differences for patients after using medical marijuana: an increase in general quality of life, mobility, and mood, with a decrease in inflammation, intraocular pressure, spasms, seizures, and pain. Results after visit 3 indicated seven significant differences compared to visit 1: decreased seizures, intraocular pressure, spasms, nausea, and pain, along with increased energy and mobility. No differences were found by patient diagnosis or age, but sex-related differences occurred in inflammation, mood, and energy. CONCLUSION: Results support positive therapeutic benefits of medical marijuana, and despite methodological limitations, our study contributes to the growing body of literature.

Cunetti, L., L. Manzo, et al. (2018). "Chronic Pain Treatment With Cannabidiol in Kidney Transplant Patients in Uruguay." Transplant Proc 50(2): 461-464.

BACKGROUND: Chronic pain is a major therapeutic problem in kidney transplant patients owing to nephrotoxicity associated with nonsteroidal antiiflammatory drugs. Benefits in chronic pain treatment with cannabidiol (CBD) have been reported. This study assesses the effect, safety, and possible drug interactions in kidney transplant patients treated with CBD for chronic pain. METHODS: We assessed patients who asked to receive CBD for pain treatment. Doses were increased from 50 to 150 mg twice a day for 3 weeks. Creatinine, blood count, liver function, liver enzymes, and drug levels were determined every 48 hours the first week and then once a week thereafter. RESULTS: We assessed 7 patients with a mean age of 64.5 years (range, 58-75 years). CBD initial dose was 100 mg/d, CBD dose reduction to 50 mg/d has been done on day 4 to patient 1 for persistent nausea. Tacrolimus dose reduction in patient 3 was undertaken on days 4, 7, and 21 owing to persisting elevated levels (even before CBD) and itching, and on day 21 in patient 5. Tacrolimus levels decreased in patient 2 but were normal in the control 1 week later. Patients on cyclosporine were stable. Adverse effects were nausea, dry mouth, dizziness, drowsiness, and intermittent episodes of heat. CBD dose decrease was required in 2 patients. Two patients had total pain improvement, 4 had a partial response in the first 15 days, and in 1 there was no change. CONCLUSIONS: During this follow-up, CBD was well-tolerated, and there were no severe adverse effects. Plasma levels of tacrolimus were variable. Therefore, longer follow-up is required.

Cuttler, C., A. Spradlin, et al. (2018). "A naturalistic examination of the perceived effects of cannabis on negative affect." Journal of Affective Disorders 235: 198-205.

Background Cannabis is commonly used to alleviate symptoms of negative affect. However, a paucity of research has examined the acute effects of cannabis on negative affect in everyday life. The current study provides a naturalistic account of perceived changes in symptoms of depression, anxiety, and stress as a function of dose and concentration of Δ9tetrahydrocannabinol (THC) and cannabidiol (CBD). Method Data from the app StrainprintTM (which provides medical cannabis users a means of tracking changes in symptoms as a function of different doses and chemotypes of cannabis) were analyzed using multilevel modeling. In total, 11,953 tracked sessions were analyzed (3,151 for depression, 5,085 for anxiety, and 3,717 for stress). Results Medical cannabis users perceived a 50% reduction in depression and a 58% reduction in anxiety and stress following cannabis use. Two puffs were sufficient to reduce ratings of depression and anxiety, while 10+ puffs produced the greatest perceived reductions in stress. High CBD (>9.5%)/low THC (<5.5%) cannabis was associated with the largest changes in depression ratings, while high CBD (>11%)/high THC (>26.5%) cannabis produced the largest perceived changes in stress. No changes in the perceived efficacy of cannabis were detected across time. However, baseline symptoms of depression (but not anxiety or stress) appeared to be exacerbated across time/tracked sessions. Limitations The primary limitations are the self-selected nature of the sample and the inability to control for expectancy effects. Conclusions Cannabis reduces perceived symptoms of negative affect in the short-term, but continued use may exacerbate baseline symptoms of depression over time.

Dagan, Y. and J. Yager (2020). "Cannabis and Complex Posttraumatic Stress Disorder: A Narrative Review With Considerations of Benefits and Harms." J Nerv Ment Dis **208**(8): 619-627.

Despite substantial controversies concerning patients' reports of benefits from cannabis for posttraumatic stress disorder (PTSD) and inconsistent research findings regarding its efficacy and adverse risks, some states have already recognized PTSD as a qualifying condition for medical cannabis. Consequently, medical cannabis can also be provided for patients with complex PTSD who experience additional posttraumatic symptoms of affective dysregulation, negative perception of the self, and difficulties in relationships due to a history of repetitive trauma. In this article, we explore cannabis use in relation to benefits versus harms that might occur relative to specific complex PTSD symptoms and comorbidities. Whereas some symptoms related to PTSD per se (e.g., anxiety, insomnia, nightmares) may be benefited, others that are more characteristic of complex PTSD (e.g., dissociation, reckless behavior, and substance abuse associated with dysregulated affect) may be aggravated. Therefore, clinicians treating patients with complex PTSD who use or seek cannabis should carefully assess patients' motivations and the impacts of particular use patterns on specific symptoms. Clinicians and patients should be aware of and fully discuss the significant number of potential adverse effects of cannabis use, several of which might impede patients' participation in beneficial psychotherapeutic, social, and medical interventions.

Dalal, R. S., S. Palchaudhuri, et al. (2020). "Preadmission Cannabis Use Is Positively Correlated With Inpatient Opioid Dose Exposure in Hospitalized Patients With Inflammatory Bowel Diseases." Inflamm Bowel Dis.

BACKGROUND: Opioid use is associated with excess mortality in patients with inflammatory bowel disease (IBD). Recent data have highlighted that inpatient opioid exposure is associated with postdischarge opioid use in this population. It is unknown if preadmission use of cannabis, which is commonly used for symptom relief among patients with IBD, increases the risk for inpatient opioid exposure when patients lack access to cannabis for symptom management. We sought to determine the association between preadmission cannabis use and inpatient opioid exposure while adjusting for relevant confounders. METHODS: We performed a retrospective cohort study of adult patients hospitalized for IBD within a large academic health system from March 1, 2017, to April 10, 2018. Opioid exposure was calculated by converting the sum of administered opioid doses to intravenous morphine milligram equivalents and dividing by length of stay. We used multivariable linear regression to assess the association between cannabis use and inpatient opioid exposure while adjusting for confounders including IBD severity and preadmission opioid use. RESULTS: Our study included 423 IBD patients. Linear regression analysis showed a significant positive correlation between inpatient opioid exposure (intravenous morphine milligram equivalents divided by length of stay) and preadmission cannabis use (coefficient = 12.1; 95% confidence interval [CI], 2.6-21.5). Other significantly associated variables were first patient-reported pain score (coefficient = 1.3; 95% CI, 0.6-2.0) and preadmission opioid use (coefficient = 22.3; 95% CI, 17.0-27.6). CONCLUSIONS: Cannabis use is positively correlated with inpatient opioid exposure after controlling for confounders. A personalized pain management approach should be considered to limit inpatient and possibly future opioid exposure among hospitalized patients with IBD who use cannabis.

Darkovska-Serafimovska, M., T. Serafimovska, et al. (2018). "Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases." J Pain Res **11**: 837-842.

Purpose: The aim of this review was to assess the efficacy of cannabis preparations for relieving pain in patients with malignant diseases, through a systematic review of randomized controlled trials (RCTs), which were predominantly double-blind trials that compared cannabis preparation to a placebo. Methods: An electronic search of all literature published until June 2017 was made in MEDLINE/PubMed, Embase, The Cochrane Controlled Trials Register and specific web pages devoted to cannabis. Results: Fifteen of the 18 trials demonstrated a significant analgesic effect of cannabinoids as compared to placebo. The most commonly reported adverse effects were generally well tolerated, mild to moderate. The main side effects were drowsiness, nausea, vomiting and dry mouth. There is evidence that cannabinoids are safe and modestly effective in neuropathic pain and also for relieving pain in patients with malignant diseases. The proportion of "responders" (patients who at the end of 2 weeks of treatment reported >/=30% reduction in pain intensity on a scale of 0-10, which is considered to be clinically important) was 43% in comparison with placebo (21%). Conclusion: The target dose for relieving pain in patients with malignant diseases is most likely about 10 actuations per day, which is about 27 mg tetrahydrocannabinol (THC) and 25 mg cannabidiol (CBD), and the highest approved recommended dose is 12 actuations per day (32 mg THC/30 mg CBD). Further large studies of cannabinoids in homogeneous populations are required.

De Aquino, J. P., M. Sherif, et al. (2018). "The Psychiatric Consequences of Cannabinoids." Clinical Therapeutics **40**(9): 1448-1456.

With rising rates of cannabis use in the general population and an increasing number of US states legalizing both recreational and medical cannabis use, it is important to be informed about the adverse consequences of cannabinoids. This Commentary provides an overview of the psychiatric effects of plant-based and synthetic cannabinoids, differentiating acute effects from effects associated with persistent use. Cannabinoids produce multiphasic and dose-dependent effects on anxiety, mood, and perception, in addition to impairing cognition and psychomotor function. Generally, in healthy individuals, the acute negative psychiatric effects of cannabinoids are rated as milder in severity compared with those in individuals with pre-existing psychiatric disorders. With chronic exposure to cannabinoids, the probability of developing tolerance and dependence can increase. A problematic pattern of cannabis use can lead to clinically significant impairment and distress. Cessation of cannabis use in individuals who are tolerant and dependent can lead to a withdrawal syndrome. Studies report long-term cannabis exposure has been linked to psychiatric disorders, such as anxiety, psychotic and mood disorders. Limitations to the existing evidence notwithstanding, the plausibility of a causal relationship between cannabinoid exposure and persistent negative psychiatric outcomes, and the potential for long-term brain changes by regular exposure, especially for adolescents, are sufficient to warrant discussions with clinicians and the public. Implications for clinicians who certify, prescribe, or care for patients receiving cannabinoids are discussed, and a case is made for further research to better understand the impact of legalization on public mental health.

De Caro, C., A. Leo, et al. (2017). "The potential role of cannabinoids in epilepsy treatment." Expert Review of Neurotherapeutics **17**(11): 1069-1079.

ABSTRACTIntroduction: Epilepsy is one of the world?s oldest recognized and prevalent neurological diseases. It has a great negative impact on patients? quality of life (QOL) as a consequence of treatment resistant seizures in about 30% of patients together with drugs? side effects and comorbidities. Therefore, new drugs are needed and cannabinoids, above all cannabidiol, have recently gathered attention.Areas covered: This review summarizes the scientific data from human and animal studies on the major cannabinoids which have been of interest in the treatment of epilepsy, including drugs acting on the endocannabinoid system.Expert commentary: Despite the fact that cannabis has been used for many purposes over 4 millennia, the development of drugs based on cannabinoids has been very slow. Only recently, research has focused on their potential effects and CBD is the first treatment of this group with clinical evidence of efficacy in children with Dravet syndrome; moreover, other studies are currently ongoing to confirm its effectiveness in patients with epilepsy. On the other hand, it will be of interest to understand whether drugs acting on the endocannabinoid system will be able to reach the market and prove their known preclinical efficacy also in patients with epilepsy.

De Ternay, J., M. Naassila, et al. (2019). "Therapeutic Prospects of Cannabidiol for Alcohol Use Disorder and Alcohol-Related Damages on the Liver and the Brain." Front Pharmacol 10: 627.

Background: Cannabidiol (CBD) is a natural component of cannabis that possesses a widespread and complex immunomodulatory, antioxidant, anxiolytic, and antiepileptic properties. Much experimental data suggest that CBD could be used for various purposes in alcohol use disorder (AUD) and alcohol-related damage on the brain and the liver. Aim: To provide a rationale for using CBD to treat human subjects with AUD, based on the findings of experimental studies. Methods: Narrative review of studies pertaining to the assessment of CBD efficiency on drinking reduction, or on the improvement of any aspect of alcohol-related toxicity in AUD. Results: Experimental studies find that CBD reduces the overall level of alcohol drinking in animal models of AUD by reducing ethanol intake, motivation for ethanol, relapse, anxiety, and impulsivity. Moreover, CBD reduces alcohol-related steatosis and fibrosis in the liver by reducing lipid accumulation, stimulating autophagy, modulating inflammation, reducing oxidative stress, and by inducing death of activated hepatic stellate cells. Finally, CBD reduces alcohol-related brain damage, preventing neuronal loss by its antioxidant and immunomodulatory properties. Conclusions: CBD could directly reduce alcohol drinking in subjects with AUD. Any other applications warrant human trials in this population. By reducing alcohol-related steatosis processes in the liver, and alcohol-related brain damage, CBD could improve both hepatic and neurocognitive outcomes in subjects with AUD, regardless of the individual's drinking trajectory. This might pave the way for testing new harm reduction approaches in AUD, in order to protect the organs of subjects with an ongoing AUD.

Desmarais, A., S. Smiddy, et al. (2020). "Evidence supporting the benefits of marijuana for Crohn's disease and ulcerative colitis is extremely limited: a meta-analysis of the literature." Annals of gastroenterology **33**(5): 495-499.

BACKGROUND: Medical marijuana is increasingly used to control inflammation and pain in inflammatory bowel disease (IBD). We performed a meta-analysis to investigate the effect of marijuana on the clinical response, induction of clinical remission, and maintenance of clinical remission compared to placebo/standard of care. METHODS: We performed a systematic search of PubMed, Embase, and Web of Science in June 2019, for cannabis/marijuana and IBD, Crohn's disease or ulcerative colitis (UC). The statistical analysis was performed using Revman (version 5.3). GRADE methodology was used to assess the quality of the evidence. RESULTS: Of the 334 studies initially reviewed, 1 trial in UC and 2 trials in Crohn's disease met eligibility. For UC, 29 patients were treated with marijuana and 31 with placebo/standard of care. There was no difference in failure to achieve clinical remission (relative risk [RR] 1.02, 95% confidence interval [CI] 0.76-1.37) or response (RR 0.99, 95%CI 0.65-1.21). Adverse events occurred in all patients receiving marijuana (RR 1.28, 95%CI 1.05-1.56). For Crohn's disease, 21 patients were treated with marijuana and 19 with placebo/standard of care. There was no difference in failure to achieve clinical remission (RR 0.72, 95%CI 0.47-1.12) or failure to achieve clinical response (RR 0.15, 95%CI 0.02-1.05). Adverse events were not reported per patient. The quality of evidence was low to very low using GRADE methodology. CONCLUSIONS: Data supporting the use of marijuana for the management of IBD are extremely limited. Further well-designed studies are needed before any positive conclusions regarding marijuana use can be drawn.

Devinsky, O., C. Verducci, et al. (2018). "Open-label use of highly purified CBD (Epidiolex(R)) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes." Epilepsy Behav **86**: 131-137.

OBJECTIVE: We studied our collective open-label, compassionate use experience in using cannabidiol (CBD) to treat epilepsy in patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes. METHODS: We included patients aged 1-30years with severe childhood-onset epilepsy who received CBD for >/=10weeks as part of multiple investigator-initiated expanded access or state access programs for a compassionate prospective interventional study: CDKL5 deficiency disorder (n=20), Aicardi syndrome (n=19), Dup15q syndrome (n=8), and Doose syndrome (n=8). These patients were treated at 11 institutions from January 2014 to December 2016. RESULTS: The percent change in median convulsive seizure frequency for all patients taking CBD in the efficacy group decreased from baseline [n=46] to week 12 (51.4% [n=35], interquartile range (IQR): 9-85%) and week 48 (59.1% [n=27], IQR: 14-86%). There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and week 12, chi(2)(2)=22.9, p=0.00001, with no difference in seizure percent change between weeks 12 and 48. Of the 55 patients in the safety group, 15 (27%) withdrew from extended observation by week 144: 4 due to adverse effects, 9 due to lack of efficacy, 1 withdrew consent, and 1 was lost to follow-up. SIGNIFICANCE: This open-label drug trial provides class III evidence for the long-term safety and efficacy of CBD administration in patients with treatment-resistant epilepsy (TRE) associated with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Adjuvant therapy with CBD showed similar safety and efficacy for these four syndromes as reported in a diverse population of TRE etiologies. This study extended analysis of the prior report from 12weeks to 48weeks of efficacy data and suggested that placebo-controlled randomized trials should be conducted to formally assess the safety and efficacy of CBD in these epileptic encephalopathies.

Devinsky, O., A. D. Patel, et al. (2018). "Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome." New England Journal of Medicine **378**(20): 1888-1897.

BACKGROUND

Cannabidiol has been used for treatment-resistant seizures in patients with severe early-onset epilepsy. We investigated the efficacy and safety of cannabidiol added to a regimen of conventional antiepileptic medication to treat drop seizures in patients with the Lennox–Gastaut syndrome, a severe developmental epileptic encephalopathy.

METHODS

In this double-blind, placebo-controlled trial conducted at 30 clinical centers, we randomly assigned patients with the Lennox–Gastaut syndrome (age range, 2 to 55 years) who had had two or more drop seizures per week during a 28-day baseline period to receive cannabidiol oral solution at a dose of either 20 mg per kilogram of body weight (20-mg cannabidiol group) or 10 mg per kilogram (10-mg cannabidiol group) or matching placebo, administered in two equally divided doses daily for 14 weeks. The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period.

RESULTS

A total of 225 patients were enrolled; 76 patients were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group. During the 28-day baseline period, the median number of drop seizures was 85 in all trial groups combined. The median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group (P=0.005 for the 20-mg cannabidiol group vs. placebo group, and P=0.002 for the 10-mg cannabidiol group vs. placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhea; these events occurred more frequently in the higher-dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial medication because of adverse events and were withdrawn from the trial. Fourteen patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations.

CONCLUSIONS

Among children and adults with the Lennox–Gastaut syndrome, the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo. Adverse events with cannabidiol included elevated liver aminotransferase concentrations. (Funded by GW Pharmaceuticals; GWPCARE3 ClinicalTrials.gov number, NCT02224560.)

Dharmapuri, S., K. Miller, et al. (2020). "Marijuana and the Pediatric Population." Pediatrics **146**: e20192629.

Cannabinoids, the psychoactive compounds in marijuana, are one of the most commonly used substances in the United States. In this review, we summarize the impact of marijuana on child and adolescent health and discuss the implications of marijuana use for pediatric practice. We review the changing epidemiology of cannabis use and provide an update on medical use, routes of administration, synthetic marijuana and other novel products, the effect of cannabis on the developing brain, other health and social consequences of use, and issues related to marijuana legalization.

Donovan, K. A., R. Oberoi-Jassal, et al. (2020). "Cannabis Use in Young Adult Cancer Patients." J Adolesc Young Adult Oncol **9**(1): 30-35.

Background: The use of cannabis by young adult (YA) cancer patients is likely to increase as medical cannabis becomes more available. Clinically relevant data on cannabis use are needed to establish benchmarks for use, to identify patients who are more likely to use cannabis, and to assess outcomes associated with use. Objective: The current study sought to determine the rate of cannabis use in YA cancer patients ages 18 to 39, identify demographic and clinical correlates of use, and examine differences in moderate-to-severe symptoms between users and nonusers. Methods: We conducted a retrospective review of objectively measured tetrahydrocannabinol (THC), self-reported cannabis use, and cancer-related symptomatology in YA cancer patients in active treatment referred for comprehensive supportive care. Results: Approximately 30% of YA cancer patients tested positive for THC on urine drug testing. At the univariate level, cannabis users were more likely to be male, to have a lifetime history of smoking at least 100 cigarettes, and to be more recently diagnosed. Cannabis use was associated with moderate-to-severe symptomatology, including pain, nausea, lack of appetite, constipation, difficulty sleeping, and poorer overall well-being. Conclusions: YAs referred for comprehensive supportive care may be managing their cancer-related symptoms with cannabis. Further research is needed to better understand patients' perceptions of cannabis's therapeutic and adverse effects, in patients who used cannabis before diagnosis, and in patients who commenced use in response to a cancer diagnosis.

Dos Reis Franco, G., S. Smid, et al. (2020). "Phytocannabinoids: General Aspects and Pharmacological Potential in Neurodegenerative Diseases." Curr Neuropharmacol.

In the last few years research into Cannabis and its constituent phytocannabinoids has burgeoned, particularly in the potential application of novel cannabis phytochemicals for the treatment of diverse illnesses related to neurodegeneration and dementia, including Alzheimer's (AD), Parkinson's (PD) and Huntington's disease (HD). To date, these neurological diseases have mostly relied on symptomatological management. However, with an aging population globally, the search for more efficient and disease-modifying treatments that could delay or mitigate disease progression is imperative. In this context, this review aims to present a state of art in the research with cannabinoids and novel cannabinoid-based drug candidates that have been emerged as novel promising alternatives for drug development and innovation in the therapeutics of a number of diseases, especially those related to CNS-disturbance and impairment.

dos Santos, R. G., J. E. C. Hallak, et al. (2017). Chapter 82 - Cannabidiol for the Treatment of Epilepsy: An Overview of Possible Mechanisms of Action and Preclinical and Human Studies A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 795-801.

Abstract Epilepsy is a neurological pathology characterized by the occurrence of seizures. There are several types of epilepsy, treated by means of several medical procedures, including antiepileptic drugs, steroids, and surgery. Antiepileptic drugs currently available do not benefit all patients, and many produce several side effects, limiting their clinical use. Cannabidiol, a natural compound present in cannabis, lacks the psychoactivity of Δ9-tetrahydrocannabinol, the main psychoactive compound in the cannabis plant. Moreover, there is in vitro and in vivo evidence that cannabidiol has anticonvulsant properties, and preliminary studies in epilepsy patients suggest that cannabidiol has antiepileptic effects, and is well tolerated. The present work introduces an overview of preclinical and human studies on the antiepileptic effects of cannabidiol, suggesting that there are sufficient preclinical and human studies to keep exploring the anticonvulsant effects of cannabidiol in randomized, controlled clinical trials.

dos Santos, R. G., J. E. C. Hallak, et al. (2017). Chapter 97 - Cannabidiol for the Treatment of Drug Use Disorders A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 939-946.

Abstract The problematic use of psychoactive substances like alcohol, cannabis, cocaine, amphetamines, heroin, and nicotine carry a series of health, economic, and social costs to individuals and society. Although pharmacological treatments for alcohol, heroin, and nicotine abuse or dependence are available, there is no approved medication for the treatment of cannabis and stimulant dependence. Cannabidiol (CBD), a nonpsychotomimetic cannabinoid present in the cannabis plant, has anxiolytic, antipsychotic, antiepileptic, and antiaddictive potentials, and is well tolerated after acute and prolonged administration. The objective of this chapter is to present an overview of the available preclinical and clinical evidence of potential antiaddictive effects of CBD. Preclinical evidence suggests that CBD has antiaddictive effects in animal models using opiates/opioids and stimulants, and preliminary studies in humans suggest that CBD reduces cigarette consumption and reduces symptoms of cannabis dependence/withdrawal. The antiaddictive effects of CBD should be investigated in randomized, place-controlled clinical trials.

Drosdowsky, A., S. Blaschke, et al. (2020). "Corrigendum to: Cancer patients' use of and attitudes towards medicinal cannabis." Australian health review : a publication of the Australian Hospital Association **44**: 656.

Objectives Access to medicinal cannabis is a timely and important issue in cancer care. Recent legislative changes in Australia have increased access to medicinal cannabis, but the views of people with cancer on this topic are poorly understood. The aim of this study was to explore the prevalence of the use of and attitudes towards medicinal cannabis among people with cancer. Methods: A cross-sectional study was performed using an anonymous, 15-item study-specific paper-based survey. The survey was administered over a 2-week period in August 2017 in the waiting rooms of a specialist cancer hospital. Results: In all, 339 patients completed the survey (mean (±s.d.) age 59±15 years; 52% male). Fourteen respondents (4%) were currently using cannabis medicinally. Only one of these respondents had a prescription for their cannabis product. Most respondents would consider using a medicinal cannabis product if recommended by their doctor (n=271; 80%). Conclusion: This study is the first of its kind to survey the use of and attitudes towards medicinal cannabis in a broad sample of Australian people with cancer. Few respondents were currently using cannabis for medicinal purposes, but an overwhelming majority were in favour of increasing access and would consider using a prescribed product. What is known about the topic? Cannabis may have a wide variety of medicinal uses, particularly in the cancer setting. Currently, people with cancer in Victoria have limited access to medicinal cannabis despite recent legislative changes. What does this paper add? In a general sample of people with cancer, few were using cannabis for medicinal purposes, but most were in favour of widening access and would consider using a product their doctor prescribed. What are the implications for practitioners? Despite supporting access, patients indicated that the recommendations of doctors and increasing the evidence base are necessary requirements to their use of medicinal cannabis.

Duffy, S. S., J. G. Lees, et al. (2018). "Managing Neuropathic Pain in Multiple Sclerosis: Pharmacological Interventions." Medicinal chemistry (Shariqah (United Arab Emirates)) **14**(2): 106-119.

BACKGROUND: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Of the plethora of motor and sensory disturbances experienced by sufferers, neuropathic pain is a highly prevalent and debilitating symptom, and at present remains extremely difficult to treat. Common forms of neuropathic pain seen in MS patients include central neuropathic pain, Lhermitte's phenomenon and trigeminal neuralgia, which are all speculated to arise from specific patterns of lesion formation.  
OBJECTIVE: Efficacious pharmacological interventions for the treatment of neuropathic pain associated with MS are lacking, and have been largely informed by drug trials in peripheral neuropathies and spinal cord injury.  
METHOD/RESULTS: Neuropathic pain in MS is inadequately relieved by conventional analgesics, and first-line therapies are generally comprised of anti-depressive and anti-convulsive drugs. A range of alternatives have been proposed and tested with variable success, including cannabinoids and certain opioid analgesics. Animals with experimental autoimmune encephalomyelitis (EAE), an autoimmune model of MS, also exhibit neuropathic pain symptoms.  
CONCLUSION: Studies aimed at understanding the mechanisms underlying EAE-induced neuropathic pain and investigating the efficacy of novel pharmacological interventions at the animal level offer an exciting area of future research, and may inform future therapeutic options for MS-associated neuropathic pain.

Dupont, J. C., K. Pritchard-Jones, et al. (2016). "Ethical issues of clinical trials in paediatric oncology from 2003 to 2013: a systematic review." Lancet Oncol **17**(5): e187-197.

A state-of-the art approach to the debates on ethical issues is key in order to gain guidance on research practices involving sick children and adolescents, as well as to identify research avenues in which it might be worth cooperating, to generate better or supplementary evidence. Based on a systematic literature search using MEDLINE, we report the main ethical developments in paediatric oncology clinical trials from 2003-13. The present knowledge about normative and empirical ethical demands in this setting is quantified and summarised in a list of 46 issues. This list primarily aims to provide readers with a comprehensive account of the main decision nodes and professional attitudes that enable families to make a safe, competent, and satisfactory decision about their child's enrolment, or non-participation, in cancer clinical trials. Our systematic Review shows how important it is for professionals to engage in a constant reflection on optimum trial designs, on the effect of offering trial participation on key family dynamics, and on the ways to understand families' needs and values accurately. In view of present scientific developments, we further emphasise the need to enhance societal awareness about research in children and adolescents, to prevent so-called research fatigue in small populations due to multiple solicitations or inadequate legal demands, and to reassess longstanding ethical certainties in the strictest view of promoting sick children's interests. This systematic Review allows a series of questions to be drawn to guide and encourage collective and individual endeavours that should lead to constant improvements in our research practices in paediatric clinical oncology research.

Edelstein, O., O. Wacht, et al. (2020). "Does Religiosity Matter? University Student Attitudes and Beliefs toward Medical Cannabis." Complementary Therapies in Medicine **51**: 102407.

Objectives To assess the relationship between religiosity and medical cannabis (MC) knowledge, attitudes and beliefs among university medical and allied health (i.e., nursing and social work) students. Methods This study uses data collected from 540 Israeli male and female, Jewish and Bedouin-Arab, religious and secular students. Pearson’s chi-squared and Fisher exact tests for categorical variables were used to determine the relationship. Results Religious, compared to secular, students reported less personal cannabis use and contact with others who use the substance. Regarding attitudes and beliefs, religious students were more likely to believe cannabis use poses serious physical and mental health risks and were less likely to recommend it for patient treatment. The majority of all students, religious and secular, believed cannabis can be addictive; are not prepared to answer patient/client MC questions; and, have not received formal education about MC. Religiosity was not found related to student knowledge about cannabis and its use for medical conditions. Conclusions This study is the first in Israel to examine the relationship between religiosity and student MC knowledge, attitudes and beliefs. Results evidence the relationship that should be used for curriculum development, education and field practice purposes linked to patient care.

Edelstein, O. E., O. Wacht, et al. (2020). "Beliefs and Attitudes of Graduate Gerontology Students about Medical Marijuana Use for Alzheimer’s and Parkinson’s Disease." Complementary Therapies in Medicine **52**: 102418.

Aims The aims of the current study were as follows: 1) to assess gerontology graduate students’ beliefs about medical marijuana’s (MMJ) effectiveness for two common age-related conditions - Alzheimer’s (AD) and Parkinson’s disease (PD); 2) to assess students’ beliefs and attitudes toward MMJ; 3) to explore associations linking background characteristics, MMJ-related attitudes and beliefs, and beliefs about the MMJ effectiveness for AD and PD. Method A sample of 104 (84 women and 20 men) gerontology graduate students voluntarily participated in the anonymous online survey. Results The vast majority (95%) of the participants indicated they had no formal education about MMJ and reported being unprepared to answer clients’ MMJ-related questions (84.6%). Most of the participants believed that MMJ is effective for use with AD (70.2%) and PD (80.8%) patients. Participants reported favorable beliefs about MMJ benefits, concerns about risks, the need for training, and positive attitudes toward recreational marijuana use legalization. Prior marijuana use (e.g., self-use, friends or family) was found to be associated with more positive beliefs about MMJ benefits, risks, and its legalization for recreational purposes. Prior marijuana use was the only factor associated with the belief that MMJ is an effective therapy for use with AD or PD patients. Conclusions The study findings show the need for students’ MMJ education in order to provide future gerontology service providers with the necessary knowledge and ability to address clients’ questions about MMJ use. Efforts to develop curricula and training programs need to be promoted.

Efron, D., K. Taylor, et al. (2020). "Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site phase I/II randomised placebo controlled trial." BMJ Open **10**(3): e034362.

Introduction Severe behavioural problems (SBPs) are a common contributor to morbidity and reduced quality of life in children with intellectual disability (ID). Current medication treatment for SBP is associated with a high risk of side effects. Innovative and safe interventions are urgently needed. Anecdotal reports and preliminary research suggest that medicinal cannabis may be effective in managing SBP in children with developmental disabilities. In particular, cannabidiol (CBD) may be a plausible and safe alternative to current medications. Families who are in urgent need of solutions are seeking cannabis for their ID children with SBP. However there is no evidence from randomised controlled trials to support the use of CBD for SBP. This pilot study aims to investigate the feasibility of conducting a randomised placebo-controlled trial of CBD to improve SBP in children with ID.Methods and analysis This is a single-site, double-blind, parallel-group, randomised, placebo-controlled pilot study of 10 participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD 20 mg/kg/day or placebo for 8 weeks. Data will be collected regarding the feasibility and acceptability of all study components, including recruitment, drop-out rate, study visit attendance, protocol adherence and the time burden of parent questionnaires. Safety outcomes and adverse events will be recorded. All data will be reported using descriptive statistics. These data will inform the design of a full scale randomised controlled trial to evaluate the efficacy of CBD in this patient group.Ethics and dissemination This protocol has received ethics approval from the Royal Children’s Hospital ethics committee (Human Research Ethics Committee no. 38236). Results will be disseminated through peer-reviewed journals, professional networks, conferences and social media.Trial registration number ACTRN12618001852246

Elliott, J., D. DeJean, et al. (2020). "Barriers in accessing medical cannabis for children with drug-resistant epilepsy in Canada: A qualitative study." Epilepsy & Behavior **111**: 107120.

Introduction The use of medical cannabis to treat drug-resistant epilepsy in children is increasing; however, there has been limited study of the experiences of parents with the current system of accessing medical cannabis for their children. Methods In this qualitative study, we used a patient-centered access to care framework to explore the barriers faced by parents of children with drug-resistant epilepsy when trying to access medical cannabis in Canada. We conducted semistructured interviews with 19 parents to elicit their experiences with medical cannabis. We analyzed the data according to five dimensions of access, namely approachability, acceptability, availability, affordability, and appropriateness. Results Parents sought medical cannabis as a treatment because of a perceived unmet need stemming from the failure of antiepileptic drugs to control their children's seizures. Medical cannabis was viewed as an acceptable treatment, especially compared with adding additional antiepileptic drugs. After learning about medical cannabis from the media, friends and family, or other parents, participants sought authorization for medical use. However, most encountered resistance from their child's neurologist to discuss and/or authorize medical cannabis, and many parents experienced difficulty in obtaining authorization from a member of the child's existing care team, leading them to seek authorization from a cannabis clinic. Participants described spending up to $2000 per month on medical cannabis, and most were frustrated that it was not eligible for reimbursement through public or private insurance programs. Conclusions Parents pursue medical cannabis as a treatment for their children's drug-resistant epilepsy because of a perceived unmet need. However, parents encounter barriers in accessing medical cannabis in Canada, and strategies are needed to ensure that children using medical cannabis receive proper care from healthcare professionals with training in epilepsy care, antiepileptic drugs, and medical cannabis.

Elliott, J., D. DeJean, et al. (2020). "Cannabis-based products for pediatric epilepsy: An updated systematic review." Seizure 75: 18-22.

Purpose To provide an up-to-date summary of the benefits and harms of cannabis-based products for epilepsy in children. Methods We updated our earlier systematic review, by searching for studies published up to May 2019. We included randomized controlled trials (RCTs) and non-randomized studies (NRS) involving cannabis-based products administered to children with epilepsy. Outcomes were seizure freedom, seizure frequency, quality of life, sleep, status epilepticus, death, gastrointestinal adverse events, and emergency room visits. Results Thirty-five studies, including four RCTs, have assessed the benefits and harms of cannabis-based products in pediatric epilepsy (12 since April 2018). All involved cannabis-based products as adjunctive treatment, and most involved cannabidiol. In the RCTs, there was no statistically significant difference between cannabidiol and placebo for seizure freedom (relative risk 6.77, 95 % confidence interval [CI] 0.36–128.38), quality of life (mean difference [MD] 0.6, 95 %CI –2.6 to 3.9), or sleep disruption (MD –0.3, 95 %CI –0.8 to 0.2). Data from both RCTs and NRS suggest that cannabidiol reduces seizure frequency and increases treatment response; however, there is an increased risk of gastrointestinal adverse events. Conclusion Newly available evidence supports earlier findings that cannabidiol probably reduces the frequency of seizures among children with drug-resistant epilepsy. PROSPERO CRD42018084755

Eskander, J. P., J. Spall, et al. (2020). "Cannabidiol (CBD) as a treatment of acute and chronic back pain: A case series and literature review." J Opioid Manag **16**(3): 215-218.

OBJECTIVE: Two patient case reports are presented describing the use of cannabidiol (CBD) for the symptomatic relief of a lumbar compression fracture and in the mitigation of thoracic discomfort and dysesthesia secondary to a surgically resected meningioma. DISCUSSION: CBD appears to have antisnociceptive and anti-inflammatory effects on opioid-naive patients with neuro-pathic and radicular pain. Of note, the patients in this case series used the same CBD cream: Baskin Essentials Body Wellness Cream (400 mg CBD per two oz.) Conclusion: Hemp-derived CBD in a transdermal cream provided significant symptom and pain relief for the patients described in this case series. Based on these results, we believe further investigation is warranted to see if CBD-containing products should have a more prominent role in the treatment of acute and chronic pain.

Esposito, G., M. Pesce, et al. (2020). "The potential of cannabidiol in the COVID-19 pandemic." British journal of pharmacology: 10.1111/bph.15157.

Identifying drugs effective in the new coronavirus disease 2019 (COVID-19) is crucial, pending a vaccine against SARS-CoV2. We suggest the hypothesis that cannabidiol (CBD), a non-psychotropic phytocannabinoid, has the potential to limit the severity and progression of the disease for several reasons:- (a) High-cannabidiol Cannabis sativa extracts are able to down-regulate the expression of the two key receptors for SARS-CoV2 in several models of human epithelia, (b) cannabidiol exerts a wide range of immunomodulatory and anti-inflammatory effects and it can mitigate the uncontrolled cytokine production responsible for acute lung injury, (c) being a PPARγ agonist, it can display a direct antiviral activity and (d) PPARγ agonists are regulators of fibroblast/myofibroblast activation and can inhibit the development of pulmonary fibrosis, thus ameliorating lung function in recovered patients. We hope our hypothesis, corroborated by preclinical evidence, will inspire further targeted studies to test cannabidiol as a support drug against the COVID-19 pandemic.

Evren, C. (2017). Chapter 8 - Cannabis Use and Cognitive Function A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 70-78.

Abstract Prevalence rates for cannabis use are steadily increasing, particularly among adolescents and young adults, which constitute a major health concern. An extensive growing body of research has demonstrated that cannabis use affects cognitive performance adversely. In particular, deficits were found in working and episodic memory, as well as in executive and attentional functions. Although some studies reported recovery with prolonged abstinence, others reported persisting impairments in several cognitive domains, such as, attention, working memory, and executive functioning. Heavy cannabis users may develop tolerance to the impairing effects of this drug on neurocognitive task performance. Age of onset, duration of use, and quantity of regular use are associated with cannabis-related impairment and recovery of neurocognitive performance. Recognition of these cognitive problems may help to select the type of the treatment. Future studies must control the potentially confounding effects of axis I disorders and other substances, and consider gender differences.

Ezechukwu, H. C., C. A. Diya, et al. (2020). "Role for endocannabinoids in early pregnancy: recent advances and the effects of cannabis use." American Journal of Physiology-Endocrinology and Metabolism **319**(3): E557-E561.

The endocannabinoid system (ECS) is associated with several physiological processes, including reproduction. This system consists of the cannabinoid receptors, endocannabinoid ligands, and enzymes that metabolize and degrade these fatty acids. Recent evidence shows that cannabinoid receptors are expressed in cells of the reproductive system, including endometrial stromal cells, ovaries, and sperm cells. Emerging and recent research suggests that the ECS may play a significant role in reproduction. The endocannabinoid ligands anandamide and 2-arachidonoylglycerol are crucial for successful endometrium decidualization, placental development, and embryo implantation. Alteration in cannabinoid receptor expression or in endocannabinoid homeostasis by excessive intake of cannabis during pregnancy is associated with negative pregnancy outcomes, including preterm birth. The use of medicinal cannabis is becoming more widespread in Western countries, especially in people of reproductive age. Cannabis contains phytocannabinoids, which modulate the ECS, and emerging evidence suggests that phytocannabinoids, through their action on cannabinoid receptors, may have a negative impact on fertility, pregnancy outcome, and fetal health. In this mini-review, we highlight the recent advances in the field, which explore the role of endocannabinoids in early pregnancy and the effects of excessive intake of phytocannabinoids in pregnancy outcomes.

Faim, J. and J. Balteiro (2020). "Cannabis Therapeutic Applications - Review." European Journal of Public Health **30**(Supplement\_2).

Introduction: Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Cannabinoids can be given orally, sublingually or topically, can be smoked, inhaled, mixed with food or made into tea. Objectives: Elaboration of a systematic literature review about cannabis’s medicinal and therapeutic properties. It is intended to characterize the plant and its properties, highlighting the proven therapeutic evidence published in the area of oncology and diseases of the central nervous system. Methodology: The selection of articles was based on the reading and analysis of the title and the abstract; only articles published in the last 15 years have been considered. After full analysis of the selected articles, it was concluded that 64 scientific articles were relevant to the study. Results: With this systematic review, we can conclude that its therapeutic application in areas such as epilepsy, multiple sclerosis and in the relief of some cancer patient’s symptoms is promising. Its apparent anti-tumour activity in various types of cancer is of increasing scientific interest as current treatments in these situations are scarce. Conclusion: The future of cannabis therapy is getting closer. It is therefore necessary to study and develop new synthetic analogues of THC, with better separation between therapeutic and side effects. Scientific advances show that Cannabis sativa is a treatment option for many conditions. With this systematic review we can conclude that its therapeutic application in areas such as epilepsy, multiple sclerosis and in the relief of some symptoms in cancer patients is promising. Its apparent anti-tumour activity in various types of cancer is also of increasing scientific interest.

Fairhurst, C., R. Kumar, et al. (2020). "Efficacy and safety of nabiximols cannabinoid medicine for paediatric spasticity in cerebral palsy or traumatic brain injury: a randomized controlled trial." Dev Med Child Neurol.

AIM: To assess the efficacy, safety, and tolerability of oromucosal nabiximols cannabinoid medicine as adjunct therapy for children with spasticity due to cerebral palsy/traumatic central nervous system injury with inadequate response to existing treatment. METHOD: Overall, 72 patients (mean [SD] age 12y 4mo [3y 1mo], range 8-18y) were randomized at a ratio of 2:1 to receive nabiximols (n=47; 29 males, 18 females) or placebo (n=25; 15 males, 10 females) for 12 weeks (12 sprays/day max. based on clinical response/tolerability). The primary outcome was change from baseline in level of spasticity on a 0 to 10 Numerical Rating Scale (NRS), assessed by the primary caregiver at 12 weeks. Secondary outcomes included additional measures for spasticity, sleep quality, pain, health-related quality of life, comfort, depression, and safety. RESULTS: There was no significant difference in the spasticity 0 to 10 NRS between nabiximols versus placebo groups after 12 weeks. No statistically significant differences were observed for any secondary endpoint. Adverse events were predominantly mild or moderate in severity; however, three cases of hallucinations were reported. INTERPRETATION: Nabiximols was generally well tolerated; however, neuropsychiatric adverse events were observed. No significant reduction in spasticity with nabiximols treatment versus placebo was observed. WHAT THIS PAPER ADDS: Oromucosal nabiximols is generally well tolerated by paediatric patients. However, three cases of hallucinations were observed, one of which involved auditory hallucinations and a suicide attempt. Oromucosal nabiximols versus placebo did not reduce cerebral palsy/central nervous system injury-related spasticity.

Farré, M., A. Farré, et al. (2017). Chapter e16 - Cannabis Use in Fibromyalgia A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** e158-e167.

Abstract Fibromyalgia is a chronic disorder characterized by widespread pain and tenderness, often accompanied by fatigue, memory problems, and sleep disturbances. Therapy includes both nonpharmacological (education, cognitive behavioral therapy, and exercise) and pharmacological treatment (including medicines as pregabalin, duloxetine, milnacipran, amitriptyline, serotonin selective reuptake inhibitors, and cyclobenzaprine). A number of surveys have reported that cannabis products are frequently used in patients with fibromyalgia. Results showed that most of the patients who tried medical marijuana found it to be effective or very effective for the therapy of some symptoms of this condition. Significant relief of pain and stiffness has been reported after cannabis self-administration. The efficacy and tolerability of oral nabilone for the treatment of pain and sleep difficulty have been established in some noncontrolled studies and two randomized-controlled clinical trials. Nabilone significantly reduced pain and improved quality of life in comparison to placebo. Nabilone was more effective than amitriptyline in improving sleep in fibromyalgia. More studies are needed to evaluate the efficacy and safety of cannabinoids in fibromyalgia.

Fedorova, E., S. Schrager, et al. (2020). "Developmental trajectories of illicit drug use, prescription drug misuse and cannabis practices among young adult cannabis users in Los Angeles." Drug and Alcohol Review.

Introduction and Aims Young adults have the highest rates of drug use and contribute significantly to the growing population of medical cannabis patients (MCP). This study examined relationships between longitudinal patterns of illicit/prescription drug use/misuse and cannabis practices among young adult cannabis users. Design and Methods In 2014–2015, 210 young adult MCP and 156 nonpatient users were recruited in Los Angeles and surveyed annually over four waves. The analytical sample was limited to completers of all four waves (n = 301). Distinct developmental trajectories of illicit drug use and prescription drug misuse were identified. Fixed effects regression analysis evaluated changes in cannabis practices by trajectory groups. Results Results supported two‐trajectory solutions (high/low) for illicit drug use and prescription drug misuse. Decreases in use within all four trajectories occurred by wave 4. Low illicit drug use trajectory members were more likely to self‐report medical cannabis use. Membership in both types of high‐use trajectories was associated with use of concentrates and edibles. The prevalence of MCP, edibles use and cannabis days decreased significantly by wave 4. Discussion and Conclusions While alternative cannabis forms use was associated with membership in high drug use trajectories, self‐reported medical cannabis use (not MCP) was negatively associated with high illicit drug use trajectory membership. Reductions in the prevalence of MCP, cannabis days, edibles use and other drug use by wave 4 alongside stable levels of self‐reported medical cannabis use might reflect the changing legal status of cannabis in California, maturing out phenomenon and safer patterns of cannabis use.

Feingold, D., S. Brill, et al. (2020). "Depression level, not pain severity, is associated with smoked medical marijuana dosage among chronic pain patients." Journal of Psychosomatic Research **135**: 110130.

Background The use of medical marijuana (MM) for the treatment of chronic pain is rapidly growing in the United States and Europe; however there is concern regarding the specificity of its therapeutic effects and the motivation underlying its use. While research indicates that among chronic pain prescribed opioids, depression has been associated with increased opioid dosage (regardless of pain levels), the extent to which depression and pain each contribute to MM dose among chronic pain patients is yet unknown. Methods This cross-sectional study included 209 chronic pain patients prescribed smoked MM, in flower or other plant form, with no concurrent opioid treatment. Ordinal regression analyses were performed in order to explore the unique contribution of mean pain level (1–10 scale), depression severity (measured by the Patient Health Questionnaire (PHQ-9)) and anxiety severity (measured by the Generalized Anxiety Disorder scale (GAD-7)) to doses of MM, while taking into account additional sociodemographic and clinical factors. Results Individuals with mild depression and those with moderate to severe depression were at significantly increased odds for using higher doses of MM in grams per month(Adjusted Odds Ratio(AOR) = 2.06,95% Confidence Interval(CI) = 1.05–4.01, and AOR = 5.95,95% CI = 1.97–17.98, respectively) compared to those without depression. In addition, individuals with mild depression were at significantly increased odds for smoking more MM joints daily(AOR = 2.07, 95% CI = 1.01–4.23) compared to individuals without depression. Mean levels of pain or anxiety severity were not significantly associated with either dose measures. Conclusions Depression and MM dose are highly correlated and should be concurrently addressed during chronic pain treatment.

Fiani, B., K. J. Sarhadi, et al. (2020). "Current application of cannabidiol (CBD) in the management and treatment of neurological disorders." Neurological Sciences.

Cannabidiol (CBD), which is nonintoxicating pharmacologically relevant constituents of Cannabis, demonstrates several beneficial effects. It has been found to have antioxidative, anti-inflammatory, and neuroprotective effects. As the medicinal use of CBD is gaining popularity for treatment of various disorders, the recent flare-up of largely unproven and unregulated cannabis-based preparations on medical therapeutics may have its greatest impact in the field of neurology. Currently, as lot of clinical trials are underway, CBD demonstrates remarkable potential to become a supplemental therapy in various neurological conditions. It has shown promise in the treatment of neurological disorders such as anxiety, chronic pain, trigeminal neuralgia, epilepsy, and essential tremors as well as psychiatric disorders. While recent FDA-approved prescription drugs have demonstrated safety, efficacy, and consistency enough for regulatory approval in spasticity in multiple sclerosis (MS) and in Dravet and Lennox-Gastaut Syndromes (LGS), many therapeutic challenges still remain. In the current review, the authors have shed light on the application of CBD in the management and treatment of various neurological disorders.

Fink, D. S., M. Stohl, et al. (2020). "Medical marijuana laws and driving under the influence of marijuana and alcohol." Addiction **115**(10): 1944-1953.

ABSTRACT Aims Medical marijuana law (MML) enactment in the United States has been associated with increased cannabis use but lower traffic fatality rates. We assessed the possible association of MML and individual-level driving under the influence of cannabis (DUIC) and also under the influence of alcohol (DUIA). Design and setting Three cross-sectional U.S. adult surveys: The National Longitudinal Alcohol Epidemiologic Survey (NLAES; 1991?1992), the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; 2001?2002), and the NESARC-III (2012?2013). Participants The total n was 118?497: 41 764, 41?184, and 35?549 from NLAES, NESARC, and NESARC-III, respectively. Measurements Across the three surveys, similar questions in the Alcohol Use Disorder and Associated Disabilities Interview Schedule assessed DUIC and DUIA. Ever-MML states enacted MML between 1991?1992 and 2012?2013 (overall period). Early-MML states enacted MML between 1991?1992 and 2001?2002 (early period). Late-MML states enacted MML between 2001?2002 and 2012?2013 (late period). MML effects on change in DUIC and DUIA prevalence were estimated using a difference-in-differences specification to compare changes in MML and other states. Findings From 1991?1992 to 2012?2013, DUIC prevalence nearly doubled (from 1.02% to 1.92%), increasing more in states that enacted MML than other states (difference-in-differences [DiD] = 0.59%; 95% CI = 0.06%?1.12%). Most change in DUIC prevalence occurred between 2001?2002 and 2012?2013. DUIC prevalence increased more in states that enacted MML 2001?2002 to 2012?2013 than in never-MML states (DiD = 0.77%; 95% CI = ?0.05%-1.59%), and in two early-MML states, California (DiD = 0.82; 95% CI = 0.06?1.59) and Colorado (DiD = 1.32; 95% CI = 0.11?2.53). In contrast, DUIA prevalence appeared unrelated to MML enactment. Conclusions Medical marijuana law enactment in US states appears to have been associated with increased prevalence of driving under the influence of cannabis, but not alcohol.

Fitzcharles, M. A., E. Rampakakis, et al. (2020). "Medical Cannabis Use by Rheumatology Patients Following Recreational Legalization: A Prospective Observational Study of 1000 Patients in Canada." ACR Open Rheumatol **2**(5): 286-293.

OBJECTIVE: Recreational legalization of cannabis may influence the medical use by patients. When only medical access was legally available in Canada, 4.3% of rheumatology patients reported use. With the current recreational legalization, we have reexamined the prevalence and characteristics of medical cannabis use in this same rheumatology setting. METHODS: Consecutively attending rheumatology patients participated in an onsite survey comprising the following two questionnaires: 1) demographic and disease information completed by the rheumatologist and 2) patient anonymous questionnaire of health status, cannabis use (recreational and/or medicinal), and characteristics of cannabis use. RESULTS: Of 1047 attendees from June to August 2019, with 1000 participating, medical cannabis had been used by 12.6% of patients (95% confidence interval 10.7%-14.8%), with half continuing use for mostly pain relief. Discontinuation was due to lack of effect in 57% of patients and side effects in 28% of patients. Ever medical users were younger (61.2 vs. 64.9 years; P = 0.006), more likely unemployed/disabled (16.7% vs. 5.9%; P < 0.001), and had more previous (47.6% vs. 25.5%; P < 0.001) and current recreational cannabis use (17.5% vs. 3.1%; P < 0.001) than nonusers. Most patients used multiple methods of administration, including smoking, vaporizing, and using oral oil preparations, but were poorly knowledgeable of product content, which was bought solely via the legal medical route by only 20%, and only one-third disclosed their use to the rheumatologist. CONCLUSION: Medical cannabis use has tripled for rheumatology patients since recreational legalization, with users being younger, not working, and having recreational cannabis experience. Concerning issues are the poor knowledge of the product being used, access via the nonmedical route, and nondisclosure to the physician.

Fraguas-Sanchez, A. I., C. Martin-Sabroso, et al. (2018). "Insights into the effects of the endocannabinoid system in cancer: a review." Br J Pharmacol 175(13): 2566-2580.

In the last few decades, the endocannabinoid system has attracted a great deal of interest in terms of its applications to clinical medicine. In particular, its applications in cancer probably represent one of the therapeutic areas with most promise. On the one hand, expression of the endocannabinoid system is altered in numerous types of tumours, compared to healthy tissue, and this aberrant expression has been related to cancer prognosis and disease outcome, suggesting a role of this system in tumour growth and progression that depends on cancer type. On the other hand, cannabinoids exert an anticancer activity by inhibiting the proliferation, migration and/or invasion of cancer cells and also tumour angiogenesis. Research update –September 2018. However, some cannabinoids, at lower concentrations, may increase tumour proliferation, inducing cancer growth. Enough data has been provided to consider the endocannabinoid system as a new therapeutic target in cancer, although further studies to fully establish the effect of cannabinoids on tumour progression are still needed.

Franklyn, A. M., J. K. Eibl, et al. (2017). "The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada." PLOS ONE **12**(11): e0187633.

Background With the Canadian government legalizing cannabis in the year 2018, the potential harms to certain populations—including those with opioid use disorder—must be investigated. Cannabis is one of the most commonly used substances by patients who are engaged in medication-assisted treatment for opioid use disorder, the effects of which are largely unknown. In this study, we examine the impact of baseline and ongoing cannabis use, and whether these are impacted differentially by gender. Methods We conducted a retrospective cohort study using anonymized electronic medical records from 58 clinics offering opioid agonist therapy in Ontario, Canada. One-year treatment retention was the primary outcome of interest and was measured for patients who did and did not have a cannabis positive urine sample in their first month of treatment, and as a function of the proportion of cannabis-positive urine samples throughout treatment. Results Our cohort consisted of 644 patients, 328 of which were considered baseline cannabis users and 256 considered heavy users. Patients with baseline cannabis use and heavy cannabis use were at increased risk of dropout (38.9% and 48.1%, respectively). When evaluating these trends by gender, only female baseline users and male heavy users are at increased risk of premature dropout. Interpretation Both baseline and heavy cannabis use are predictive of decreased treatment retention, and differences do exist between genders. With cannabis being legalized in the near future, physicians should closely monitor cannabis-using patients and provide education surrounding the potential harms of using cannabis while receiving treatment for opioid use disorder.

Freeman, J. L. (2018). "Safety of cannabidiol prescribed for children with refractory epilepsy." Med J Aust **209**(5): 228-229.

Cannabidiol as an add-on therapy is reported to reduce convulsive seizures in patients with Dravet syndrome and to reduce drop seizures in patients with Lennoxe Gastaut syndrome. Twenty children aged 2-17 years (median, 10 years) were treated for 9-40 weeks (median, 23 weeks) between February and November 2017 with a state-sponsored cannabidiol product(CBD Max [Tilray]: 98% cannabidiol in grapeseed oil100 mg/mL). Cannabidiol is still a pharmaceutical in development, with potential benefits that require further delineation, and with short term adverse effects that must be understood and mitigated.

Furrer, D., E. Kröger, et al. (2020). Cannabis against chronic muskuloskeletal pain: A scoping review on users and their perceptions.

Background Chronic musculoskeletal pain (CMP) may lead to reduced physical function and is the most common cause of chronic non cancer pain. Currently, the pharmacotherapeutic options against CMP are limited and mainly consist of pain management with gabapentinoids or opioids, which carry major adverse effects. Although the effectiveness of medical cannabis (MC) for CMP still lacks solid evidence, several patients suffering from it are exploring this therapeutic option. Objectives Little is known about MC users suffering from CMP. We aimed to increase this knowledge, useful for health care professionals and policy makers considering this treatment, as well as for researchers planning rigorous randomized clinical trials on the effectiveness of MC. Methods We conducted a scoping literature review, according to the methods developed by Arksey and O’Malley, to describe the views and perceptions of patients who had consumed MC to relieve chronic CMP and other non-cancer pain, as well as their demographic characteristics, patterns of MC use, and perceived positive and negative effects. Conclusion Our review shows that MC users are frequently young or middle-aged men, and that the preferred form of use was smoking. Participants of the included studies reported that MC use was helpful in reducing CMP and other chronic non-cancer pain with only minor adverse effects; in addition, they reported improved psychological well-being. Discussion The information from the included studies has several methodological limitations and is exploratory. MC use might, from the perspective of persistent users suffering from CMP and other chronic non-cancer pain, produce more benefits than harms. However, specific results for CMP are very scarce.

Fusar-Poli, L., V. Cavone, et al. (2020). Cannabinoids for People with ASD: A Systematic Review of Published and Ongoing Studies.

The etiopathogenesis of autism spectrum disorder (ASD) remains largely unclear. Among other biological hypotheses, researchers have evidenced an imbalance in the endocannabinoid (eCB) system, which regulates some functions typically impaired in ASD, such as emotional responses and social interaction. Also, cannabidiol (CBD), the non-intoxicating component of Cannabis sativa, has been recently approved for treatment-resistant epilepsy. Seizures represent frequent medical comorbidities of ASD and could be responsible for the onset or worsening of behavioral problems. Thus, it has been hypothesized that cannabinoids could be useful in improving some ASD symptoms. Our systematic review was conducted according to the PRISMA guidelines and aimed to summarize the literature regarding the use of cannabinoids in ASD. After searching in Web of KnowledgeTM, PsycINFO, and Embase, we included ten studies (eight papers and two abstracts). Four ongoing trials were retrieved in ClinicalTrials.gov. Findings are promising, as cannabinoids appeared to improve problem behaviors, sleep, hyperactivity, and communication deficits, with limited cardiac and metabolic side effects. Interestingly, they generally allowed to reduce the number of prescribed medications and decreased the frequency of seizures in epileptic patients. Mechanisms of action could be linked to the excitatory/inhibitory imbalance found in people with ASD. However, further trials need to be implemented with better characterization and homogenization of samples, and well-defined outcomes.

Gali, K., R. Narode, et al. (2020). "Online patient-provider cannabis consultations." Prev Med **132**: 105987.

Cannabis has been legalized, decriminalized, or medicalized in over half the U.S. states. With restrictions on cannabis research, accepted standards to guide clinical practice are lacking. Analyzing online communications through a digital health platform, we characterized patient questions about cannabis use and provider responses. Coded for content were 4579 questions posted anonymously online between March 2011 through January 2017, and the responses from 1439 U.S. licensed clinicians. Provider responses to medical cannabis use questions were coded for sentiment: "negative", "positive", and "mixed." Responses could be "thanked" by patients and receive "agrees" from providers. The most frequent themes were detection of cannabis use (25.3%), health harms (19.9%), co-use with other substances (9.1%), and medical use (8.2%). The 425 medical cannabis use questions most frequently related to treatment of mental illness (20.3%), pain (20.0%), and cancer care (6.7%). The 762 provider responses regarding medical cannabis use were coded for sentiment as 59.6% negative, 28.6% mixed, and 11.8% positive. Provider sentiment was most positive regarding cannabis use for palliative care and most negative for treating respiratory conditions, poor appetite, and mental illness. The proportion of positive sentiment responses increased from 17.6% to 32.4%. Provider responses coded as negative sentiment received more provider "Agrees" (mean rank = 280) than those coded as positive (mean rank = 215), beta coefficient = 0.33; 95% CI: 0.05, 0.62; p = .02. Cannabis use is a health topic of public interest. Variability in provider responses reflects the need for more research and consensus building to inform evidence-based clinical guidelines for cannabis use in medicine.

Gamelin, F. X., G. Cuvelier, et al. (2020). "Cannabidiol in sport: Ergogenic or else?" Pharmacol Res **156**: 104764.

In the sports domain, cannabis is prohibited by the World Anti-Doping Agency (WADA) across all sports in competition since 2004. The few studies on physical exercise and cannabis focused on the main compound i.e. Delta9-tetrahydrocannabinol. Cannabidiol (CBD) is another well-known phytocannabinoid present in dried or heated preparations of cannabis. Unlike Delta9-tetrahydrocannabinol, CBD is non-intoxicating but exhibits pharmacological properties that are interesting for medical use. The worldwide regulatory status of CBD is complex and this compound is still a controlled substance in many countries. Interestingly, however, the World Anti-Doping Agency removed CBD from the list of prohibited substances - in or out of competition - since 2018. This recent decision by the WADA leaves the door open for CBD use by athletes. In the present opinion article we wish to expose the different CBD properties discovered in preclinical studies that could be further tested in the sport domain to ascertain its utility. Preclinical studies suggest that CBD could be useful to athletes due to its anti-inflammatory, analgesic, anxiolytic, neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, almost no clinical data are available on CBD in the context of exercise, which makes its use in this context still premature.

Gandor, F. and G. Ebersbach (2017). "Cannabinoids in the Treatment of Parkinson’s Disease." **01**: E307-E311.

Due to the changing legal status of medical cannabis and derivatives in numerous countries,this therapeutic option has moved into the field of public debate. Neurologists treating patients with idiopathic Parkinson’s disease are increasingly confronted with questions regarding cannabis as a treatment alternative, especially for levodopa-resistant Parkinson’s symptoms. A number of single case reports and case series suggested improvement of Parkinsonian symptoms after cannabinoid intake, but the small number of available randomized clinical trials failed to reproduce the extent of these findings. Only one trial found a reduction of levodopa-induced dyskinesia with cannabinoid treatment, the remaining three trials showed no effect on Parkinsonian symptoms. This article gives an overview on the effects of cannabis, and reviews experimental and clinical trials studying the effects of cannabinoids in idiopathic Parkinson’s disease.

Garcia, J. M. and T. A. Shamliyan (2018). "Cannabinoids in Patients with Nausea and Vomiting Associated with Malignancy and Its Treatments." Am J Med 131(7): 755-759.e752.

Cannabis-based medications (cannabinoids) have been approved by the US Food and Drug Administration (FDA) for the treatment of adults with chemotherapy-induced nausea. However, some guidelines do not recommend these drugs as a useful therapeutic option for patients with inadequate response to commonly used antiemetic agents. Reimbursement of cannabinoids for medical purposes varies across countries, although patient satisfaction and adherence are high. We conducted a rapid review according to an a priori–developed protocol to examine the most current evidence about the benefits and harms of cannabinoids in patients with nausea and vomiting associated with malignancy and its treatments.

Gaston, T. E., J. B. Allendorfer, et al. (2020). "Effects of highly purified cannabidiol (CBD) on fMRI of working memory in treatment-resistant epilepsy." Epilepsy & Behavior **112**: 107358.

Objective We aimed to determine changes in working memory and functional connectivity via functional magnetic resonance imaging (fMRI)-modified Sternberg task after treatment with highly purified cannabidiol (CBD, Epidiolex®; 100 mg/mL) in patients with treatment-resistant epilepsy (TRE). Methods Twenty patients with TRE (mean age: 35.8 years; 7 male) performed fMRI Sternberg task before receiving CBD (“PRE”) and after reaching stable dosage of CBD (15–25 mg/kg/day; “ON”). Each patient performed 2 runs of the modified Sternberg task during PRE and ON fMRI. Twenty-three healthy controls (HCs; mean age: 25 years; 11 M) also completed the task. All were presented with a sequence of 2 or 6 letters and instructed to remember them (encoding). After a delay, a single letter was shown, and participants recalled if letter was shown in sequence (retrieval). Paired t-tests were used to analyze accuracy/response times. For each subject, event-related modeling of encoding (2 and 6 letters) and retrieval was performed. Paired t-tests controlling for seizure frequency change and scanner type were performed to assess changes in neural recruitment during encoding and retrieval in key regions of interest. Results There was nonsignificant increase in mean modified Sternberg task accuracy from PRE to ON-CBD (28.6 vs. 32.1%). PRE and ON accuracy was worse than HCs (75.5%, p < 0.001). ON-PRE comparison revealed increased activation in the right inferior frontal gyrus (IFG) during 6-letter encoding. ON-HC comparison revealed increased activation in bilateral IFG and insula during 2-letter encoding. PRE-HC comparison revealed decreased activation in the left middle frontal gyrus during 6-letter encoding. None of these activations were associated with working memory performance. Significance Treatment-resistant epilepsy results in poorer working memory performance and lower neural recruitment compared with HCs. Treatment with CBD results in no significant changes in working memory performance and in significant increases in neural activity in regions important for verbal memory and attention compared with HCs during memory encoding.

Gericke, M. and D. Hartmann (2018). "[A Lot of Hot Steam: the Cannabinoid Hyperemesis Syndrome]." Dtsch Med Wochenschr **143**(16): 1182-1185.

HISTORY: The 43-year-old patient was admitted because of vomiting and abdominal pain. He had a history of depression and multiple discus prolapses. He reported the consumption of three beers per day. FINDINGS: The patient presented diffuse abdominal pain. The serume-kreatine was elevated (205 micromol/l), there was a leucocytosis (18,4^3/microl) and a mild elevation of y-GT (2,3microkat/l). Stool culture was negative. An abdominal ultrasound and a gastroscopy did not show groundbreaking findings. THERAPY AND COURSE: The acute kidney injury was treated by administration of intravenous fluid. The vomiting persisted despite of administration of Metoclopramid and Dimenhydrinat. Just Lorazepam and hot showers brought relief of symptoms. A decided drug history revealed marijuana abuses. After ceasing marijuana consumption and administration of Haloperidol the vomiting stopped. CONCLUSIONS: The cannabinoid hyperemesis syndrome is characterized by vomiting, diffuse abdominal pain and taking hot showers. With typical combination of symptoms a drug history should be taken. The knowledge of this syndrome can help to avoid over-diagnostic.

Gherzi, M., G. Milano, et al. (2020). "Safety and pharmacokinetics of medical cannabis preparation in a monocentric series of young patients with drug resistant epilepsy." Complementary Therapies in Medicine **51**: 102402.

Objectives To evaluate safety and pharmacokinetic parameters (PK) of medical cannabis in add-on for children and young adults with drug-resistant epilepsy. Design, setting Ten patients (4 females, 6 males, age 2.5–23.2 years) were enrolled in a prospective open trial with a galenic preparation (decoction) of Italian cannabis (FM2, ratio THC:CBD = 3:5, range THC 5.2–7.2 %; CBD 8.2–11.1 %). Patients received the first dose in Hospital, progressively augmented by CBD dose titration (from 1 to 4 mg/kg/day). Outcome measures In order to assess safety, blood parameters, heart rates and electrocardiograms (ECGs) were evaluated before the enrollment and during the follow up. The PK study was performed measuring THC and CBD concentrations by UHPLC–MS/MS in plasma samples collected during the first administration and at each follow-up visit. Results Two out of ten patients stopped the treatment for adverse events (detected in 6/10: gastroenteric, sleep or behavioral disorders) and difficulties in drug supply. We observed minor ECG alterations in two patients and asymptomatic transient reductions of fibrinogen after 6 months of therapy. The PK study during follow-up revealed statistically significant correlations between THC-CBD blood concentrations and: volumes of decoction, FM2 and THC-CBD daily dosages. Conclusions The present study, although with some limitations, shows a good safety profile of medical cannabis in children and young patients with drug-resistant epilepsy and encourages the possibility of further studies with oral cannabis-based drugs. The correlations between THC-CBD plasma concentrations and their administered dosages underline the need of a therapeutic drug monitoring for cannabinoids therapy.

Giacoppo, S., P. Bramanti, et al. (2017). "Sativex in the management of multiple sclerosis-related spasticity: An overview of the last decade of clinical evaluation." Multiple Sclerosis and Related Disorders **17**: 22-31.

Background Spasticity is a common symptom of multiple sclerosis (MS) affecting about 80% of MS patients. Numerous lines of evidence suggest that spasticity due to its complexity is not adequately managed with conventional anti-spastic therapies. Therefore, in order to improve the outcomes for the majority of MS patients, alternative approaches are needed to be discovered. Over the last years, the use of cannabinoid compounds as a potential treatment for MS-related symptoms has aroused great interest, owing to encouraging preclinical and clinical studies. To date, Sativex, an oromucosal spray containing tetrahydrocannabinol and cannabidiol in approximately 1:1 ratio, is the only commercially available formulation containing cannabinoids used as add-on therapy for treatment of spasticity in adult MS patients who are not responding to conventional antispastic therapies. Methods Here, by performing a literature search, we provided an overview of the last decade of clinical evaluations as well as post-marketing studies about effectiveness and safety of Sativex in the management of MS-related spasticity. Results Sativex was proven effective in treating spasticity and also in improving the patient's quality of life. In addition, a low incidence of adverse reactions Sativex-related supports the good safety profile and its tolerability. Conclusion This review by recognizing the clinical effectiveness of Sativex in spasticity management, opened a new opportunity for many patients with spasticity resistant to common antispastic drugs.

Good, P. D., R. M. Greer, et al. (2020). "An Open-Label Pilot Study Testing the Feasibility of Assessing Total Symptom Burden in Trials of Cannabinoid Medications in Palliative Care." Journal of palliative medicine **23**(5): 650-655.

Background: There is considerable interest in the use of cannabinoids for symptom control in palliative care, but there is little high-quality evidence to guide clinical practice. Objectives: Assess the feasibility of using global symptom burden measures to assess response to medicinal cannabis, to determine median tolerated doses of cannabidiol (CBD) and tetrahydrocannabinol (THC), and to document adverse events (AEs). Design: Prospective two-arm open-label pilot trial of escalating doses of CBD and THC oil. Setting/Subjects: Participants had advanced cancer and cancer-related symptoms in a palliative and supportive care service in an Australian cancer center. Measurements: The main outcome measures were the number of participants screened and randomized over the time frame, the number of participants completing days 14 and 28 and providing total symptom distress scores (TSDSs) (measured using the Edmonton Symptom Assessment Scale), and the change from baseline of the TSDS at day 14. Results: Of the 21 participants enrolled (CBD, n = 16; THC, n = 5), 18 (86%) completed the primary outcome measure at day 14 and 8 completed at day 28. The median maximum tolerated doses were CBD, 300 mg/day (range 100-600 mg); THC, 10 mg/day (range 5-30 mg). Nine of 21 patients (43%) met the definition of response (≥6 point reduction in TSDS). Drowsiness was the most common AE. Conclusions: Trials of medicinal cannabis in advanced cancer patients undergoing palliative care are feasible. The doses of THC and CBD used in this study were generally well tolerated and the outcome measure of total symptom distress is promising as a measure of overall symptom benefit. Trial registration: ACTRN12618001205224.

Gonzalez-Cuevas, G., R. Martin-Fardon, et al. (2018). "Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle." Neuropsychopharmacology **43**(10): 2036-2045.

Cannabidiol (CBD), the major non-psychoactive constituent of Cannabis sativa, has received attention for therapeutic potential in treating neurologic and psychiatric disorders. Recently, CBD has also been explored for potential in treating drug addiction. Substance use disorders are chronically relapsing conditions and relapse risk persists for multiple reasons including craving induced by drug contexts, susceptibility to stress, elevated anxiety, and impaired impulse control. Here, we evaluated the "anti-relapse" potential of a transdermal CBD preparation in animal models of drug seeking, anxiety and impulsivity. Rats with alcohol or cocaine self-administration histories received transdermal CBD at 24 h intervals for 7 days and were tested for context and stress-induced reinstatement, as well as experimental anxiety on the elevated plus maze. Effects on impulsive behavior were established using a delay-discounting task following recovery from a 7-day dependence-inducing alcohol intoxication regimen. CBD attenuated context-induced and stress-induced drug seeking without tolerance, sedative effects, or interference with normal motivated behavior. Following treatment termination, reinstatement remained attenuated up to approximately 5 months although plasma and brain CBD levels remained detectable only for 3 days. CBD also reduced experimental anxiety and prevented the development of high impulsivity in rats with an alcohol dependence history. The results provide proof of principle supporting potential of CBD in relapse prevention along two dimensions: beneficial actions across several vulnerability states and long-lasting effects with only brief treatment. The findings also inform the ongoing medical marijuana debate concerning medical benefits of non-psychoactive cannabinoids and their promise for development and use as therapeutics.

Good, P., A. Haywood, et al. (2019). "Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD)." BMC Palliative Care 18(1): 110.

Despite improvements in medical care, patients with advanced cancer still experience substantial symptom distress. There is increasing interest in the use of medicinal cannabinoids, but there is little high quality evidence to guide clinicians. This study aims to define the role of cannabidiol (CBD) in the management of symptom burden in patients with advanced cancer undergoing standard palliative care.

Greger, J., V. Bates, et al. (2020). "A Review of Cannabis and Interactions With Anticoagulant and Antiplatelet Agents." J Clin Pharmacol **60**(4): 432-438.

Legalization of medical cannabis has occurred in 33 states and the District of Columbia, and recreational use has increased exponentially since 2013. As a result, it is important to understand how cannabis interacts with other drugs and has potential risks for patients on concomitant medications. Components of medical cannabis can inhibit or compete for several cytochrome P450 (CYP) hepatic isoenzymes, UDP-glucuronosyltransferases, and P-glycoprotein. These enzymes and transporters are involved in the metabolism and absorption of numerous medications, including anticoagulants (ACs) and antiplatelet agents (APs), potentially causing harmful drug-drug interactions. ACs and/or APs are often prescribed to high-risk patients with cardiac conditions, a history of myocardial infarction, or stroke. Cannabis may cause these medications to be less efficacious and put patients at risk for recurrent cardiovascular and cerebrovascular events. Several case reports show cannabis may inhibit the metabolism of warfarin because of CYP2C9 interactions, resulting in increased plasma concentrations, increased international normalized ratio, and risk of bleeding. Cannabidiol inhibits CYP2C19, an isoenzyme responsible for the transformation of clopidogrel to its active thiol metabolite. This interaction could lead to subtherapeutic levels of active metabolite and possibly increased stroke risk. Within this review, a total of 665 articles were screened from PubMed and EMBASE. Four case reports, 1 in vitro study, and 1 pharmacokinetic article were found to be of relevance. This review serves to examine reported and potential cannabis interactions with APs/ACs to help inform patients and health care providers of possible risks and knowledge gaps.

Groh, C. J. (2020). "Medical Cannabis and Psychiatric Disorders: Implications for Psychiatric Nurses." J Am Psychiatr Nurses Assoc: 1078390320945791.

OBJECTIVE: Cannabis use for medical condition has significantly increased over the past 20 years with 33 states and the District of Columbia passing laws legalizing medical cannabis. Five qualifying psychiatric disorders have been identified. The objective of this review article is to present a brief history of medical cannabis, the evidence for the qualifying psychiatric conditions, and to discuss the implications for psychiatric nurses. METHOD: A review of the literature on the five qualifying psychiatric disorders was conducted. Databases searched included CINAHL, PubMed, Cochrane Library, MedLine Plus, and EMBASE. Keywords were cannabis, medical cannabis, delta-9-tetrahydrocannabinaol, cannabidiol, and psychiatric disorders. RESULTS: The evidence that medical cannabis or cannabinoids is an effective treatment for the qualifying psychiatric disorders (e.g., posttraumatic stress disorder, agitation in Alzheimer's disease and other dementias, Tourette's syndrome, anxiety, and obsessive-compulsive disorder) is too weak and of low quality to recommend as an intervention at this time. A discussion of the implications of these findings for psychiatric nurses is offered based on the published guidelines by the American Nurses Association and National Council of State Boards of Nursing. CONCLUSION: There is a significant gap between evidence supporting the effectiveness of medical cannabis for psychiatric disorders and patient interest and use of cannabis for such conditions as well as other psychiatric symptoms. There are tremendous opportunities for psychiatric nurses to make an impact both clinically and be conducting research in this emerging field. We need to educate ourselves and our patients about the benefits and risks of medical cannabis and to help patients make informed decisions about their health care.

Gruber, S. A., K. A. Sagar, et al. (2017). "The Grass Might Be Greener: Medical Marijuana Patients Exhibit Altered Brain Activity and Improved Executive Function after 3 Months of Treatment." Frontiers in Pharmacology **8**: 983.

The vast majority of states have enacted full or partial medical marijuana (MMJ) programs, causing the number of patients seeking certification for MMJ use to increase dramatically in recent years. Despite increased use of MMJ across the nation, no studies thus far have examined the specific impact of MMJ on cognitive function and related brain activation. In the present study, MMJ patients seeking treatment for a variety of documented medical conditions were assessed prior to initiating MMJ treatment and after 3 months of treatment as part of a larger longitudinal study. In order to examine the effect of MMJ treatment on task-related brain activation, MMJ patients completed the Multi-Source Interference Test (MSIT) while undergoing functional magnetic resonance imaging (fMRI). We also collected data regarding conventional medication use, clinical state, and health-related measures at each visit. Following 3 months of treatment, MMJ patients demonstrated improved task performance accompanied by changes in brain activation patterns within the cingulate cortex and frontal regions. Interestingly, after MMJ treatment, brain activation patterns appeared more similar to those exhibited by healthy controls from previous studies than at pre-treatment, suggestive of a potential normalization of brain function relative to baseline. These findings suggest that MMJ use may result in different effects relative to recreational marijuana (MJ) use, as recreational consumers have been shown to exhibit decrements in task performance accompanied by altered brain activation. Moreover, patients in the current study also reported improvements in clinical state and health-related measures as well as notable decreases in prescription medication use, particularly opioids and benzodiapezines after 3 months of treatment. Further research is needed to clarify the specific neurobiologic impact, clinical efficacy, and unique effects of MMJ for a range of indications and how it compares to recreational MJ use.

Gupta, N., M. A. McDonald, et al. (2020). "Cannabis Use and Heart Transplantation: A Canadian Perspective." The Journal of Heart and Lung Transplantation **39**(4, Supplement): S263-S264.

Purpose Although cannabis was legalized in Canada until October 2018, there is no clear consensus among the heart transplant community with respect to transplant eligibility among cannabis users. We sought to determine prevailing attitudes towards cannabis use in heart transplant candidates amongst healthcare professionals in Canada, and to determine whether there are differences compared to jurisdictions where cannabis has not been legalized. Methods A voluntary and independent web-based survey was distributed to members of the Canadian Cardiac Transplant Network. The survey questions were based on previous work by Neyer and colleagues who conducted a similar multi-national survey in 2016. Results There were a total of 38 providers representing 15 adult and paediatric transplant programs across the country that provided responses to assess current opinions and attitudes in regards to cannabis use and heart transplantation. Fifty-two percent of the respondents were in favour of listing patients who consumed medical cannabis, while only 5% were against listing, and 43% would only consider transplant listing with additional stipulations. This is less limiting compared to 35.6% of respondents in the 2016 survey conducted by Neyer et all who found listing patients who consumed medical cannabis unfavourable. Twenty-one percent of respondents were against listing patients who consumed recreational cannabis, which is again markedly less than the 72.5% of respondents from Neyer's survey. Sixty-seven percent did not believe that patients who consume cannabis legally through inhalation methods should be listed for transplant, while only 5% of respondents were against listing for patients who consume cannabis through oral ingestion. Conclusion In the current Canadian context of legalized cannabis, there is heterogeneity of attitudes towards transplant eligibility depending on route of ingestion and pattern of use. Compared to other nations, Canadian health care providers may have less restrictive attitudes towards listing cannabis users for cardiac transplantation. Current attitudes towards cannabis use in transplant candidates should inform further research and guideline development.

Habib, G. and U. Levinger (2019) Medical Cannabis in Treatment of Resistant Familial Mediterranean Fever. The American journal of case reports 20, 1340-1342 DOI: 10.12659/ajcr.917180

BACKGROUND Colchicine-resistant familial Mediterranean fever can be treated by anti-IL-1 biologic therapy; however, such treatment needs approval by the health insurance company, and many patients are denied such treatment or do not respond to it. CASE REPORT Two familial Mediterranean fever (FMF) patients, both homozygous for M694V mutation and resistant to colchicine treatment, were treated with medical cannabis. Prior to that, 1 patient was denied biologic treatment and the other had no significant response to anakinra. Under medical cannabis treatment, both patients had remarkable improvement in the severity of the attacks and also a decrease in the frequency of the attacks, from once every 2 weeks to 1 attack every month in 1 patient; this patient had also a remarkable reduction in the C-reactive protein level during the attacks. CONCLUSIONS Cannabis is a therapeutic option for treating the most complex patients with FMF.

Habib, G. and S. Artul (2018). "Medical Cannabis for the Treatment of Fibromyalgia." J Clin Rheumatol **24**(5): 255-258.

BACKGROUND: Fibromyalgia is a chronic pain syndrome, characterized by chronic musculoskeletal pain, fatigue, and mood disturbances. There are nearly no data on the effect of medical cannabis (MC) treatment on patients with fibromyalgia. METHODS: Data were obtained from the registries of 2 hospitals in Israel (Laniado Hospital and Nazareth Hospital) on patients with a diagnosis of fibromyalgia who were treated with MC. After obtaining patient consent, demographic, clinical, and laboratory parameters were documented. All the patients also completed the Revised Fibromyalgia Impact Questionnaire regarding the period before and after MC treatment. RESULTS: Thirty patients were identified, and 26 patients were included in the study. There were 19 female patients (73%), and the mean age of the study group was 37.8 +/- 7.6 years. The mean dosage of MC was 26 +/- 8.3 g per month, and the mean duration of MC use was 10.4 +/- 11.3 months. After commencing MC treatment, all the patients reported a significant improvement in every parameter on the questionnaire, and 13 patients (50%) stopped taking any other medications for fibromyalgia. Eight patients (30%) experienced very mild adverse effects. CONCLUSIONS: Medical cannabis treatment had a significant favorable effect on patients with fibromyalgia, with few adverse effects.

Habib, G. and I. Avisar (2018). The Consumption of Cannabis by Fibromyalgia Patients in Israel.

Objective To report on the habits of cannabis consumption among fibromyalgia patients in Israel. Patients and Methods An Internet-based questionnaire was posted to three large fibromyalgia Facebook groups in our country. The questionnaire was anonymous and included demographic, clinical, and cannabis-related questions, including acquisition of a license for medical cannabis (MC) method and amount of cannabis consumption; need to buy cannabis beyond the medical allowance; effect of cannabis on pain, sleep, depression, and anxiety; adverse effects of cannabis; feelings of dependence on cannabis or other meds; the involvement of family members; tendency to drive after using cannabis; and employment and social disability status. Results Of 2,705 people, 383 (14%) responded to the questionnaire, with a mean age of 42.2±14.2 years. Of the responders, 84% reported consuming cannabis, and 44% were licensed for MC. The mean amount per month of cannabis consumed was 31.4±16.3g, and 80% of cannabis consumers (CC) smoked pure cannabis or cannabis mixed with tobacco. Pain relief was reported by 94% of CC, while 93% reported improved sleep quality, 87% reported improvement in depression, and 62% reported improvement in anxiety. Of MC-licensed CC, 55% bought cannabis beyond the medical allowance on the black market. Adverse effects were reported by 12% of CC. Only 8% reported dependence on cannabis. Most CC (64%) worked either full- or part-time jobs, and 74% reported driving “as usual” under cannabis use. Conclusions Cannabis consumption among fibromyalgia patients in our country is very common and is mostly not licensed. Nearly all CC reported favorable effects on pain and sleep, and few reported adverse effects or feeling of dependence on cannabis.

Hahn, B. (2018). "The Potential of Cannabidiol Treatment for Cannabis Users With Recent-Onset Psychosis." Schizophrenia Bulletin **44**(1): 46-53.

A major factor associated with poor prognostic outcome after a first psychotic break is cannabis misuse, which is prevalent in schizophrenia and particularly common in individuals with recent-onset psychosis. Behavioral interventions aimed at reducing cannabis use have been unsuccessful in this population. Cannabidiol (CBD) is a phytocannabinoid found in cannabis, although at low concentrations in modern-day strains. CBD has a broad pharmacological profile, but contrary to ∆9-tetrahydrocannabinol (THC), CBD does not activate CB1 or CB2 receptors and has at most subtle subjective effects. Growing evidence indicates that CBD acts as an antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. Moreover, CBD attenuates THC’s detrimental effects, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the disease trajectory of individuals with early psychosis and comorbid cannabis misuse in particular—a population with currently poor prognostic outcome and no specialized effective intervention.

Haleem, R. and R. Wright (2020). "A Scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults." Journal of clinical medicine research **12**(6): 344-351.

Indications of cannabis use are numerous although the indication to relief pain remains a major research interest and clinical application. Studies investigating the effect of herbal cannabis and cannabis-based medicine on neuropathic, non-neuropathic pain, acute pain and experimentally induced pain were reviewed. A search was performed in PubMed and Cochrane library for articles published in English between January 1, 2000 and May 8, 2020. The search terms used were related to cannabis and pain in adults. We identified 34 studies, of which 30 were randomized controlled clinical trials (RCTs). Varying effects were identified from the RCTs, and as expected more promising effects from non-RCTs. Cannabis-based medications were found most effective as an adjuvant therapy in refractory multiple sclerosis, and weak evidence was found to support the treatment of cancer pain especially in advanced stages. Chronic rheumatic pain showed promising results. Adverse events of cannabis-based treatment were found to be more frequent with tetrahydrocannabinol herbal strains compared to other cannabis-derived products.

Hall, W., R. West, et al. (2018). "It is premature to expand access to medicinal cannabis in hopes of solving the US opioid crisis." Addiction 113(6): 987-988.

There is very weak evidence to support the claim thatexpanding access to medical cannabis will reduce opioidoverdose deaths in the United States.All human beings are susceptible to conﬁrmatory bias, inthat we are inclined to uncritically accept evidence that ac-cords with our pre-existing beliefs [1]. A good example isthe preparedness of some researchers to accept weak evi-dence that increased access to medical cannabis in theUnited States has reduced opioid overdose deaths in that country.

Hansra, D. M. (2017). "Evaluation of safety, efficacy, and other clinical endpoints of delta-9-tetrahydrocannabinol in older patients with hem/onc malignancies." Journal of Clinical Oncology **35**(15\_suppl): e21671-e21671.

e21671Background: Dronabinol, synthetic delta-9-tetrahydrocannabinol (?-9-thc), is the active compound & natural occuring component of Cannabis Sativa L(Marijuana). Dronabinol is used as an appetite stimulant & treatment of chemo induced nausea/vomiting in cancer patients (pts). Here we evaluate the efficacy, safety, & other clinical endpoints in older cancer pts. Methods: Survey study administered to cancer pts prescribed Dronabinol w/ 7 questions (yes/no/n/a): Did Dronabinol increase appetitie? decrease nausea/vomiting? improve mood? decrease insomnia? decrease anxiety? have any side effects? improve quality of life (QOL)? Also pts were asked if they preferred sythetic meds vs natural plant based meds (oil, capsule, liquid, etc). Inclusion: age > 60, hem/onc malignancy, prescribed Dronabinol. Exclusion: death, altered mental status, not taking Dronabinol, off label use. Unpaired t-test w/ two sided P value used to compare differences. Results: N = 28 pts enrolled, 12 pts excluded, 16 pts meeting study criteria. Mean age 70 (range 61-78). 100% white pts w/ 94% Latin 6% non-Latin. 50% male 50% female. 81% Onc vs 19% Heme malignancy. Dose given: 2.5 mg QD (25%), 2.5 mg BID (62.5%), 5mg BID (12.5%). Significant improvements in appetite (87.5% vs 12.5% p = < 0.0001), anxiety (75% vs 25% p = 0.0128), QOL (81.3% vs 18.7% p = 0.0001) observed. No side effects seen in 87.5 % vs 12.5% (dizziness) p = < 0.0001 of pts. 100% vs 0%, p = < 0.0001 of pts preferred natural plant based meds vs synthetics. Non significant improvements in mood (61.5% vs 38.5% p = 0.2567), insomnia (61.5% vs 38.5% p = 0.2567), nausea/vomiting (71.4% vs 28.6% p = 0.1263) observed. Conclusions: This unique study shows Dronabinol significantly improved appetite, anxiety, & QOL in older cancer pts w/ most pts having no side effects. Also non significant improvements in mood, nausea/vomiting, insomnia observed. 100% of pts preferred natural plant based meds vs. synthetics. Further investigations examining the clinical benefits & safety of Dronabinol & Cannabis Sativa L are warranted in older cancer patients.

Hardy, J., A. Haywood, et al. (2020). "Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo-controlled, randomised clinical trial of efficacy and safety of 1:1 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)." Trials **21**(1): 611-611.

BACKGROUND: Despite improvements in medical care, patients with advanced cancer still experience substantial symptom distress. There is increasing interest in the use of medicinal cannabinoids but little high-quality evidence to guide clinicians. This study aims to define the role of a 1:1 delta-9-tetrahydrocannabinol/cannabidiol (THC/CBD) cannabinoid preparation in the management of symptom burden in patients with advanced cancer undergoing standard palliative care. METHODS AND DESIGN: One hundred fifty participants will be recruited from five sites within the Queensland Palliative Care Research Group (QPCRG) and randomly assigned to an active treatment or placebo group. This study is a pragmatic multicentre, randomised, placebo-controlled, two-arm trial of escalating doses of an oral 1:1 THC/CBD cannabinoid preparation. It will compare efficacy and safety outcomes of a titrated dose (10 mg/10 mg/mL oral solution formulation, dose range 2.5 mg/2.5 mg-30 mg/30 mg/day) against placebo. There is a 2-week patient-determined titration phase, using escalating doses of 1:1 THC/CBD or placebo, to reach a dose that achieves symptom relief with tolerable side effects. This is then followed by a further 2-week assessment period on the stable dose determined in collaboration with clinicians. The primary objective is to assess the effect of escalating doses of a 1:1 THC/CBD cannabinoid preparation against placebo on change in total symptom score, with secondary objectives including establishing a patient-determined effective dose, the change in total physical and emotional sores, global impression of change, anxiety and depression, opioid use, quality of life and adverse effects. DISCUSSION: This will be the first placebo-controlled clinical trial to rigorously evaluate the efficacy, safety and acceptability of 1:1 THC/CBD for symptom relief in advanced cancer patients. This study will allow the medical community to have some evidence to present to patients wishing to access cannabis for their symptoms caused by advanced malignancy. TRIAL REGISTRATION: ACTRN, ACTRN12619000037101 . Registered on 14 January 2019. Trial Sponsor: Mater Misericordiae Limited (MML) and Mater Medical Research Institute Limited (MMRI)-Raymond Terrace, South Brisbane, Brisbane, QLD, Australia.

Hauser, N., T. Sahai, et al. (2016). "High on Cannabis and Calcineurin Inhibitors: A Word of Warning in an Era of Legalized Marijuana." Case Reports in Transplantation **2016**: 4028492.

Tacrolimus, a potent immunosuppressant medication, acts by inhibiting calcineurin, which eventually leads to inhibition of T-cell activation. The drug is commonly used to prevent graft rejection in solid organ transplant and graft-versus-host disease in hematopoietic stem cell transplant patients. Tacrolimus has a narrow therapeutic index with variable oral bioavailability and metabolism via cytochrome P-450 3A enzyme. Toxicity can occur from overdosing or from drug-drug interactions with the simultaneous administration of cytochrome P-450 3A inhibitors and possibly P-glycoprotein inhibitors. Tacrolimus toxicity can be severe and may include multiorgan damage. We present a case of suspected tacrolimus toxicity in a postallogeneic hematopoietic stem cell transplant patient who was concurrently using oral marijuana. This case represents an important and growing clinical scenario with the increasing legalization and use of marijuana throughout the United States.

Hawkins, M. N. and T. L. Horvath (2017). "Cannabis in fat: high hopes to treat obesity." The Journal of Clinical Investigation **127**(11): 3918-3920.

Cannabinoid receptor type-1 (CB1) is known to have a substantial impact on the regulation of energy metabolism via central and peripheral mechanisms. In this issue of the JCI, Ruiz de Azua and colleagues provide important insights into the regulation of adipocyte physiology by CB1. Mice with adipocyte-specific deletion of the CB1-encoding gene had an overall improved metabolic profile in addition to reduced body weight and total adiposity. These changes were associated with an increase in sympathetic tone of the adipose tissue and expansion of activated macrophages, both of which occurred prior to changes in body weight, lending support to a causal relationship between loss of CB1 in adipocytes and systemic metabolic changes. This work identifies adipocyte CB1s as a potential novel peripheral target for affecting systemic metabolism with diminished CNS effects.

Heng, M., M. F. McTague, et al. (2018). "Patient Perceptions of the Use of Medical Marijuana in the Treatment of Pain After Musculoskeletal Trauma: A Survey of Patients at 2 Trauma Centers in Massachusetts." Journal of Orthopaedic Trauma **32**(1): e25-e30.

Objective: To evaluate musculoskeletal trauma patients' beliefs regarding the usefulness of marijuana as a valid medical treatment for postinjury and postoperative pain and anxiety. Design: Prospective survey. Setting: Two academic Level 1 trauma centers. Patients/Participants: Five hundred patients in an orthopedic outpatient clinic. Intervention: Survey. Main Outcome Measurements: (1) Do patients believe that marijuana can be used as medicine? (2) Do patients believe that marijuana can help treat postinjury pain? (3) Are patients comfortable speaking with their health care providers about medical marijuana? Results: The majority of patients felt that marijuana could be used to treat pain (78%, 390) and anxiety (62%, 309). Most patients (60%, 302) had used marijuana at least once previously, whereas only 14% reported using marijuana after their injury. Of those who used marijuana during their recovery, 90% (63/70) believed that it reduced symptoms of pain, and 81% (57/70) believed that it reduced the amount of opioid pain medication they used. Conclusions: The majority of patients in this study believed that medical marijuana is a valid treatment and that it does have a role in reducing postinjury and postoperative pain. Those patients who used marijuana during their recovery felt that it alleviated symptoms of pain and reduced their opioid intake. Our results help inform clinicians regarding the perceptions of patients with trauma regarding the usefulness of marijuana in treating pain and support further study into the utility of medical marijuana in this population.

Hergenrather, J. Y., J. Aviram, et al. (2020). "Cannabinoid and Terpenoid Doses are Associated with Adult ADHD Status of Medical Cannabis Patients." Rambam Maimonides Med J **11**(1).

OBJECTIVE: The aim of this cross-sectional questionnaire-based study was to identify associations between the doses of cannabinoids and terpenes administered, and symptoms of attention deficit hyperactivity disorder (ADHD). METHODS: Participants were adult patients licensed for medical cannabis (MC) treatment who also reported a diagnosis of ADHD by a physician. Data on demographics, ADHD, sleep, and anxiety were collected using self-report questionnaires. Data collected on MC treatment included administration route, cultivator, cultivar name, and monthly dose. Comparison statistics were used to evaluate differences in reported parameters between low (20-30 g, n=18) and high (40-70 g, n=35) MC monthly dose and low adult ADHD self-report scale (ASRS, 0-5) score (i.e. </=3.17 score, n=30) or high ASRS score (i.e. >/=3.18 score, n=29) subgroups. RESULTS: From the 59 patients that answered the questionnaire, MC chemovar could be calculated for 27 (45%) of them. The high MC monthly dose group consumed higher levels of most phyto-cannabinoids and terpenes, but that was not the case for all of the cannabis components. The high dose consumers and the ones with lower ASRS score reported a higher occurrence of stopping all ADHD medications. Moreover, there was an association between lower ASRS score subgroup and lower anxiety scores. In addition, we found an association between lower ASRS score and consumption of high doses of cannabinol (CBN), but not with Delta-9-tetrahydrocannabinol (THC). CONCLUSION: These findings reveal that the higher-dose consumption of MC components (phyto-cannabinoids and terpenes) is associated with ADHD medication reduction. In addition, high dosage of CBN was associated with a lower ASRS score. However, more studies are needed in order to fully understand if cannabis and its constituents can be used for management of ADHD.

Herlopian, A., E. J. Hess, et al. (2020). "Cannabidiol in treatment of refractory epileptic spasms: An open-label study." Epilepsy & Behavior **106**: 106988.

Objective This study aimed to evaluate clinical efficacy and safety of purified pharmaceutical cannabidiol (CBD) as an adjunctive therapy in refractory childhood-onset epileptic spasms (ES). Methods Nine patients with ES were enrolled in an Institutional Review Board (IRB)- and Food and Drug Administration (FDA)-approved expanded access investigational new drug trial. Patients received plant-derived highly purified CBD in oral solution in addition to their baseline medications at an initial dosage of 5 mg/kg/day, which was increased by 5 mg/kg/day every week to an initial target dosage of 25 mg/kg/day. Seizure frequency, adverse event, and parents' subjective reports of cognitive and behavioral changes were recorded after 2 weeks and 1, 2, 3, 6, 9, and 12 months of CBD treatment. Responder rates (percent of patients with >50% reduction in ES frequency from baseline) were calculated. Electrographic changes were studied in relation to CBD initiation and clinical response. Results Overall, the responder rates in 9 patients were 67%, 78%, 67%, 56%, 78%, 78%, and 78% after 2 weeks and 1, 2, 3, 6, 9, and 12 months of CBD treatment, respectively. Three out of nine patients (33%) were ES free after two months of treatment. Parents reported subjective improvements in cognitive and behavioral domains. Side effects, primarily drowsiness, were seen in 89% of patients (n = 8). Eight of the nine (89%) patients had electroencephalographic (EEG) studies prior to and after initiation of CBD. Three out of five patients (60%) had resolution in their hypsarrhythmia pattern. Significance Purified pharmaceutical CBD may be an effective and safe adjunctive therapy in refractory ES and may also be associated with improvements in electrographic findings.

Hernandez-Folgado, L. (2017). Chapter 67 - Pharmacological Aspects of Novel Antiobesity Agents Related to Cannabinoids A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 649-658.

Abstract Obesity is a complex metabolic disorder characterized by an imbalance in energy homeostasis, abnormal increase of adipose tissue, and dysregulation of hormones, cytokines, and other important signaling systems. The increasing prevalence of overweight and obesity is associated with many diet-related chronic diseases, including diabetes mellitus, hepatic steatosis, cardiovascular risk, sleep apnea, stroke, hypertension, and certain cancers. This disease is characterized by leptin and insulin resistance, and appears to be associated with a dysregulated and hyperactive endocannabinoid system, in rodents and humans. Animal studies and clinical trials have shown that blockade of CB1 cannabinoid receptor induces weight loss, improves cardiometabolic risk factors and insulin resistance, and causes metabolic benefits in mammals. Then, blockade of CB1 receptor is considered a challenged strategy in obesity. Thus, the design, molecular structure and pharmacology of novel CB1 antagonists and CB1 inverse agonists are being reported. Moreover, novel cannabinoid targets to develop antiobesity drugs, such as CB2 cannabinoid receptor, the putative cannabinoid GPR55 receptor, and 2-monoacylglycerol lipase, are being taken into account.

Herzog, S., M. Shanahan, et al. (2018). "Systematic Review of the Costs and Benefits of Prescribed Cannabis-Based Medicines for the Management of Chronic Illness: Lessons from Multiple Sclerosis." PharmacoEconomics **36**(1): 67-78.

Cannabis-based medicines (CBMs) may offer relief from symptoms of disease; however, their additional cost needs to be considered alongside their effectiveness. We sought to review the economic costs and benefits of prescribed CBMs in any chronic illness, and the frameworks used for their economic evaluation.

Hill, K. P. and M. D. Palastro (2017). "Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts." Polish archives of internal medicine **127**(11): 785-789.

Recently, many countries have enacted new cannabis policies, including decriminalization of cannabis possession as well as legalization of medical and recreational cannabis. In this context, patients and their physicians have had an increasing number of conversations about the risks and benefits of cannabis. While cannabis and cannabinoids continue to be evaluated as pharmacotherapy for medical conditions, the best evidence currently exists for the following medical conditions: chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis. We also reviewed the current state of evidence for cannabis and cannabinoids for several other medical conditions, while addressing the potential acute and chronic effects of cannabis use, which are issues that physicians must consider before making an official recommendation on the use of medical cannabis to a patient. As the number of patient requests for medical cannabis has been increasing, physicians must become knowledgeable on the science of medical cannabis and open to a discussion about why the patient feels that medical cannabis may be helpful.

Ho, W. S. V. and M. E. M. Kelly (2017). Chapter Ten - Cannabinoids in the Cardiovascular System. Advances in Pharmacology. D. Kendall and S. P. H. Alexander, Academic Press. **80:** 329-366.

Cannabinoids are known to modulate cardiovascular functions including heart rate, vascular tone, and blood pressure in humans and animal models. Essential components of the endocannabinoid system, namely, the production, degradation, and signaling pathways of endocannabinoids have been described not only in the central and peripheral nervous system but also in myocardium, vasculature, platelets, and immune cells. The mechanisms of cardiovascular responses to endocannabinoids are often complex and may involve cannabinoid CB1 and CB2 receptors or non-CB1/2 receptor targets. Preclinical and some clinical studies have suggested that targeting the endocannabinoid system can improve cardiovascular functions in a number of pathophysiological conditions, including hypertension, metabolic syndrome, sepsis, and atherosclerosis. In this chapter, we summarize the local and systemic cardiovascular effects of cannabinoids and highlight our current knowledge regarding the therapeutic potential of endocannabinoid signaling and modulation.

Holtkamp, M. and M. Hamerle (2017). Chapter 44 - Cannabis Use in Epilepsy—Risks and Benefits A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 431-438.

Abstract Cannabis and some of its compounds—cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC)—have long been discussed regarding their pro- and anticonvulsant properties. Results of most animal models are in favor for seizure suppressing or preventing effects of CBD and THC. Available clinical data commonly support these findings. However, level of clinical evidence is low and mainly based on four underpowered randomized placebo-controlled trials, case reports, and surveys on patients and their proxies. Safety and tolerability of CBD in medical use so far seems to be favorable as well, while THC exhibits psychoactive adverse events which—at least in children—may have some clinical significance. Potential immunosuppressive effects and interactions with specific antiepileptic drugs need particular attention. In summary, current findings argue for the use of cannabis in chronic epilepsy, but there is an urgent need for high-quality randomized controlled trials on efficacy and safety of cannabis compounds in this patient cohort.

Hostiuc, S., A. Moldoveanu, et al. (2018). "The Association of Unfavorable Traffic Events and Cannabis Usage: A Meta-Analysis." Frontiers in Pharmacology **9**(99).

Background. In the last years were published many epidemiological articles aiming to link driving under the influence of cannabis with the risk of various unfavorable traffic events, with sometimes contradictory results. Aim. The primary objective of this study was to analyse whether there is a significant association between druving under the influence of cannabis and unfavorable traffic events. Materials and methods. We used two meta-analytical methods to assess the statistical significance of the effect size: random effects model and inverse variance heterogeneity model. Results. 24 studies were included in the meta-analysis. we obtained significant increases in the effect size for driving under the influence of cannabis tested through blood analysis, with an Odds Ratio (OR) of 1.27 and a Confidence Interval (CI) between 1.36-3.80, death as an outcome, with an OR of 1.56, and a CI between 1.16 and 2.09, and case-control as the type of study, with an OR of 1.99 and a CI between 1.05 and 3.80. Publication bias was very high. Conclusion. Our analysis suggests that the overall effect size for driving under the influence of cannabis on unfavorable traffic events is not statistically significant, but there are significant differences obtained through subgroup analysis. This result might be caused by either methodological flaws (which are often encountered in articles on this topic), the indiscriminate employment of the term “cannabis use” or an actual absence of an adverse effect. When a driver is found, in traffic, with a positive reaction suggesting cannabis use, the result should be corroborated by either objective data regarding marijuana usage (like blood analyses, with clear cut-off values), or a clinical assessment of the impairment, before establishing his/her fitness to drive.

Hsu, K., E. Whitham, et al. (2019). "Potential role of cannabidiol for seizure control in a patient with recurrent glioma." Journal of Clinical Neuroscience.

Glioma-related epilepsy significantly impact on patients’ quality of life, and can often be difficult to treat. Seizures cause significant morbidity for example neurocognitive deterioration, which may result from seizures themselves or due to adverse effects from antiepileptic drugs. Management of tumour with surgery, radiotherapy and chemotherapy may contribute to seizure control, but tumour related epilepsy is often refractory despite adequate treatment with standard anti-epileptic medications. Given the increasing interest in medicinal cannabis (or cannabidiol or CBD) as an anti-epileptic drug, CBD may help with seizure control in glioma patients with treatment-refractory seizures. Here we present a case of a young lady with recurrent glioma who had refractory seizures despite multiple anti-epileptic agents, who had significant benefit with CBD.

Hussain, S. A., D. J. Dlugos, et al. (2020). "Synthetic pharmaceutical grade cannabidiol for treatment of refractory infantile spasms: A multicenter phase-2 study." Epilepsy & Behavior 102: 106826.

Purpose Limited data suggest that cannabidiol (CBD) may be effective for treatment of refractory infantile spasms (IS). This study was designed to more rigorously evaluate the efficacy and safety of synthetic CBD in the treatment of IS. Methods Children six to 36 months of age with IS that failed treatment with both adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) were eligible for enrollment. Children receiving clobazam were excluded. After baseline overnight video-electroencephalography (vEEG) to confirm diagnosis and ascertain hypsarrhythmia, patients were treated with synthetic CBD oral solution (20 mg/kg/day). Overnight video-EEG was repeated after 14 days, and both baseline and repeat video-EEGs were completely de-identified and reviewed in a pairwise fashion by an independent, blinded pediatric electroencephalographer. The primary efficacy endpoint was freedom from spasms and hypsarrhythmia on day 14. Results Nine patients were enrolled, comprising an older (median age = 23 months) cohort with long-standing IS (median duration = 13 months) and numerous prior treatment failures (median = 6). One patient responded to therapy and eight patients exhibited neither clinical nor electrographic response. Conclusions The immediate but temporary response in a single patient suggests that CBD oral solution is not particularly effective in highly refractory cases, but may, nevertheless, be effective in younger patients with shorter durations of IS. Further study, examining both short- and long-term outcomes, is warranted to further evaluate the efficacy and safety of CBD oral solution in the treatment of IS.

Hyunjung, C., H. D. Scott, et al. (2017). "Medical Marijuana and Crime: Substance Use and Criminal Behaviors in a Sample of Arrestees." Journal of Drug Issues **48**(2): 182-204.

After decades of prohibition, laws allowing marijuana use for medical and, in some cases, recreational purposes have been enacted across the country. To date, however, little is known about medical marijuana use, particularly regarding its relationship to criminal offending and use by nonauthorized persons. The current study bridges this gap by examining offending patterns in a sample of recent arrestees in Maricopa County, Arizona, identified and interviewed through the Arizona Arrestee Reporting Information Network (AARIN) project. Findings suggest that medical users had a higher probability for committing Driving Under the Influendce (DUI) and drug selling/making than nonusers, and diverted medical marijuana users had a higher probability for involvement in property crime, violent crime, DUI, and drug selling/making than nonusers. The results have important implications for developing marijuana decriminalization policies, criminal justice, and criminological theory. Directions for future research are discussed.

Inglet, S., B. Winter, et al. (2020). "Clinical Data for the Use of Cannabis-Based Treatments: A Comprehensive Review of the Literature." Ann Pharmacother **54**(11): 1109-1143.

OBJECTIVE: To compile and synthesize the available literature describing medical cannabis use across various disease states. DATA SOURCES: PubMed, EBSCO, and Google Scholar searches were conducted using MeSH and/or keywords. STUDY SELECTION AND DATA EXTRACTION: Studies were included if they described the use of cannabis-based products and medications in the treatment of a predefined list of disease states in humans and were published in English. The extraction period had no historical limit and spanned through April 2019. DATA SYNTHESIS: Evidence was compiled and summarized for the following medical conditions: Alzheimer disease, amyotrophic lateral sclerosis, autism, cancer and cancer-associated adverse effects, seizure disorders, human immunodeficiency virus, inflammatory bowel disease, multiple sclerosis (MS), nausea, pain, posttraumatic stress disorder, and hospice care. RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: Based on identified data, the most robust evidence suggests that medical cannabis may be effective in the treatment of chemotherapy-induced nausea and vomiting, seizure disorders, MS-related spasticity, and pain (excluding diabetic neuropathy). Overall, the evidence is inconsistent and generally limited by poor quality. The large variation in cannabis-based products evaluated in studies limits the ability to make direct comparisons. Regardless of the product, a gradual dose titration was utilized in most studies. Cannabis-based therapies were typically well tolerated, with the most common adverse effects being dizziness, somnolence, dry mouth, nausea, and euphoria. CONCLUSIONS: As more states authorize medical cannabis use, there is an increasing need for high-quality clinical evidence describing its efficacy and safety. This review is intended to serve as a reference for clinicians, so that the risks and realistic benefits of medical cannabis are better understood.

Ishida, J. H., P. O. Wong, et al. (2019). "Substitution of marijuana for opioids in a national survey of US adults." PLOS ONE 14(10): e0222577.

Opioid prescriptions for chronic pain and subsequent opioid-related complications have risen dramatically in the US. Recent data suggest that medical marijuana laws have been associated with lower state-level opioid overdose mortality. In a national survey, we examined the prevalence of substitution of marijuana for opioids among US adults taking opioids for pain.Using GfK’s KnowledgePanel, we conducted an Internet-based survey of a nationally representative sample of 16,280 adults in 2017 about individual perceptions and use of marijuana. We developed questions designed to assess the extent and reasons for substitution of marijuana for opioids. We examined opioid substitution among respondents with a history of ever using marijuana who used opioids in the past 12 months. There were 9,003 respondents, corresponding to a 55.3% response rate. The mean age was 48 years. Among the 5% (n = 486) who reported ever using marijuana and using opioids in the past year, 43% used opioids daily, and 23% reported current (past 30 day) marijuana use. Forty-one percent reported a decrease or cessation of opioid use due to marijuana use; 46% reported no change in opioid use; and 8% reported an increase in opioid use. We found that a substantial number of US adults reported that they substituted marijuana for opioids.

Izquierdo, G. (2017). "Multiple sclerosis symptoms and spasticity management: new data." Neurodegenerative Disease Management **7**(6s): 7-11.

Spasticity, perceived by patients as muscle rigidity and spasms, is a common symptom in multiple sclerosis (MS). It is associated with functional impairment that can exacerbate other MS symptoms and reduce quality of life. Pharmacological treatment options are limited and frequently ineffective. Treatment adherence is a key issue to address in these patients. The efficacy and safety of 9-delta-tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray for treatment of MS spasticity were demonstrated in four Phase III trials. Observational studies and registry data subsequently confirmed the effectiveness and tolerability of THC:CBD oromucosal spray under everyday practice conditions. Among patients who respond to treatment, THC:CBD oromucosal spray has been shown to produce positive improvements in gait parameters and to normalize muscle fibers.

James Huntsman, R., R. Tang-Wai, et al. (2018). "Cannabis for the treatment of paediatric epilepsy? An update for Canadian paediatricians." Paediatrics & Child Health: pxy036-pxy036.

The plant Cannabis sativa produces over 140 known cannabinoids. These chemicals generate considerable interest in the medical research community for their possible application to several intractable disease conditions. Recent reports have prompted parents to strongly consider Cannabis products to treat their children with drug resistant epilepsy. Physicians, though, are reluctant to prescribe Cannabis products due to confusion about their regulatory status and limited clinical data supporting their use. We provide the general paediatrician with a brief review of cannabinoid biology, the literature regarding their use in children with drug resistant epilepsy, the current Health Canada and Canadian Paediatric Society recommendations and also the regulations from the physician regulatory bodies for each province and territory. Given the complexities of conducting research on Cannabis products for children with epilepsy, we also discuss outstanding research objectives that must be addressed to support Cannabis products as an accepted treatment option for children with refractory epilepsy.

Jarjou'i, A. and G. Izbicki (2020). "Medical Cannabis in Asthmatic Patients." Isr Med Assoc J **22**(4): 232-235.

BACKGROUND: With the increased use of cannabis in the medicinal and recreational domains, it is becoming more important for physicians to better understand its harmful and beneficial effects. Although medical cannabis comes in several forms, the preferred route of administration is smoking or inhalation. After caring for three asthmatic patients who were treated with medical cannabis and who reported improvement in their symptoms, we decided to review the available data on the effects of medical cannabis on asthmatic patients. OBJECTIVES: To review the known effects of medical cannabis on asthmatic patients. METHODS: A thorough search was conducted of the MEDLINE and PubMed databases as well as the internet for publications about the effects of medical cannabis on asthmatic patients. RESULTS: Cannabis has a bronchodilator effect on the airways and might have an anti-inflammatory effect on asthmatic patients. However, harmful effects on the lungs are mainly attributed to smoking and include airway irritation and the development of chronic bronchitis symptoms. CONCLUSIONS: Cannabis has some benefit, yet there are many harmful effects on the lungs. Additional research is needed to determine the harmful effects of vaporizers as well as inhalers.

Johal, H., T. Devji, et al. (2020). "Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis." Clin Med Insights Arthritis Musculoskelet Disord **13**: 1179544120906461.

Background: For patients with chronic, non-cancer pain, traditional pain-relieving medications include opioids, which have shown benefits but are associated with increased risks of addiction and adverse effects. Medical cannabis has emerged as a treatment alternative for managing these patients and there has been a rise in the number of randomized clinical trials in recent years; therefore, a systematic review of the evidence was warranted. Objective: To analyze the evidence surrounding the benefits and harms of medical cannabinoids in the treatment of chronic, non-cancer-related pain. Design: Systematic review with meta-analysis. Data sources: Medline, Embase, CINAHL, SCOPUS, Google Scholar, and Cochrane Databases. Eligibility criteria: English language randomized clinical trials of cannabinoids for the treatment of chronic, non-cancer-related pain. Data extraction and synthesis: Study quality was assessed using the Cochrane risk of bias tool. All stages were conducted independently by a team of 6 reviewers. Data were pooled through meta-analysis with different durations of treatment (2 weeks, 2 months, 6 months) and stratified by route of administration (smoked, oromucosal, oral), conditions, and type of cannabinoids. Main outcomes and measures: Patient-reported pain and adverse events (AEs). Results: Thirty-six trials (4006 participants) were included, examining smoked cannabis (4 trials), oromucosal cannabis sprays (14 trials), and oral cannabinoids (18 trials). Compared with placebo, cannabinoids showed a significant reduction in pain which was greatest with treatment duration of 2 to 8 weeks (weighted mean difference on a 0-10 pain visual analogue scale -0.68, 95% confidence interval [CI], -0.96 to -0.40, I (2) = 8%, P < .00001; n = 16 trials). When stratified by route of administration, pain condition, and type of cannabinoids, oral cannabinoids had a larger reduction in pain compared with placebo relative to oromucosal and smoked formulations but the difference was not significant (P[interaction] > .05 in all the 3 durations of treatment); cannabinoids had a smaller reduction in pain due to multiple sclerosis compared with placebo relative to other neuropathic pain (P[interaction] = .05) within 2 weeks and the difference was not significant relative to pain due to rheumatic arthritis; nabilone had a greater reduction in pain compared with placebo relative to other types of cannabinoids longer than 2 weeks of treatment but the difference was not significant (P[interaction] > .05). Serious AEs were rare, and similar across the cannabinoid (74 out of 2176, 3.4%) and placebo groups (53 out of 1640, 3.2%). There was an increased risk of non-serious AEs with cannabinoids compared with placebo. Conclusions: There was moderate evidence to support cannabinoids in treating chronic, non-cancer pain at 2 weeks. Similar results were observed at later time points, but the confidence in effect is low. There is little evidence that cannabinoids increase the risk of experiencing serious AEs, although non-serious AEs may be common in the short-term period following use.

Johal, H., C. Vannabouathong, et al. (2020). "Medical cannabis for orthopaedic patients with chronic musculoskeletal pain: does evidence support its use?" Therapeutic Advances in Musculoskeletal Disease **12**: 1759720X20937968.

The treatment of chronic, non-cancer musculoskeletal pain has become a topic growing interest as it is believed to be one of the reasons for the current opioid epidemic. The medicinal use of cannabis has a long history as a number of active compounds in cannabis have been shown to interact with the body’s endocannabinoid system to reduce pain. This position paper provides a history on the evolution of cannabis, the science behind its therapeutic effects, and review of the evidence and current guideline recommendations on its use as a treatment for patients with chronic, non-cancer musculoskeletal pain. Results from systematic reviews have demonstrated a statistically significant reduction in chronic pain conditions with cannabinoids, compared with placebo, although the effects might be considered small and did not reach the minimally important difference. More adverse events were reported in the cannabinoid group than in the placebo group with longer than 2 weeks of treatment. There is a lack of evidence on dependence. With changes to policies, patients’ perception has changed to be more positive toward the use of medical cannabis. Current recommendations from North America, Latin America, Europe, Australia and Iran support the use of medical cannabis for chronic, non-cancer pain. Based on the current evidence, it is our position that cannabinoids may be considered as an adjunctive therapy after recommended first- and second-line therapies have failed to provide sufficient efficacy or tolerability. Patients should consider the balance between the desirable and undesirable effects of taking cannabis for chronic pain, and comprehensively consider their own values and preferences, as well as cost-effectiveness factors, based on the information provided by their physician.

Jugl, S., S. Keshwani, et al. (2020). "A systematic review of evidence for cannabis and cannabinoids as adjuvant therapy in palliative and supportive oncology care." Journal of Clinical Oncology **38**: 12091-12091.

12091 Background: Medical cannabis use is increasing significantly in the United States as states reduce restrictions. However, ambiguity concerning the evidence for medical cannabis efficacy and safety, especially in the field of oncology, is persistent. Clinicians therefore face challenges in examining benefits and risks of medical cannabis as adjuvant treatment for cancer patients. This study identifies and evaluates the most recent available evidence for the efficacy of cannabis and cannabinoids as adjuvant in supportive and/or palliative use in patients with cancer. Methods: Electronic databases searched included PubMed, Embase, Web of Science, and Cochrane Library to identify studies published following the latest available systematic review, between July 2016 through October 2019. Studies conducted outside the United States, studies not evaluating cannabis or cannabinoids in Oncology care, and preclinical studies were excluded. Findings were organized in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework. Lastly, qualitative synthesis was used to generate summary statements about the role of cannabis and cannabinoids as adjuvant in supportive and/or palliative cancer care. Results: We screened 2,267 articles and included 96 studies in our qualitative synthesis. Among those were 2 RCT’s (1 completed), 6 Systematic reviews with Meta-analysis, 4 Systematic reviews without Meta-analysis, 71 other types of reviews and 13 observational studies. The most frequently reported outcomes assessed were efficacy of cannabis and cannabinoids for: pain (40 of 96; 17 indicating improvement), nausea and vomiting (26 of 96; 20 indicating improvement), cachexia (22 of 96; 2 indicating improvement), and utilization patterns of cannabis and/or cannabinoids among cancer patients (8 of 96). Conclusions: Latest available prevalence estimates indicate that a significant proportion of patients in the United States with cancer use cannabis and/or cannabinoids (18.3-40.0%). There is substantial evidence for the effectiveness of cannabis and cannabinoids in treating cancer-related pain; specifically, oromucosal THC/CBD spray. There is conclusive evidence for the effectiveness of cannabis and cannabinoids in relieving chemotherapy-induced nausea and vomiting; specifically, oral THC. There is inconclusive evidence regarding the effectiveness of cannabis and cannabinoids in treating cancer-related cachexia.

Kaasbøll, C., R. Hagen, et al. (2018). "Population-Based Associations Among Cannabis Use, Anxiety, and Depression in Norwegian Adolescents." Journal of Child & Adolescent Substance Abuse **27**(4): 238-243.

ABSTRACTObjective: The aim of the study was to explore the use of cannabis among Norwegian adolescents and examine associations with self-reported symptoms of anxiety and depression, age, and dose/frequency of use. Methods: A total of 36,714 Norwegian adolescents between the ages of 13 and 17 completed a cross-sectional national survey. Results: Cannabis users reported significantly more symptoms of anxiety and depression compared to non-users. There were no significant differences on anxiety and depression scores between those who had tried the drug once and those who had tried it six times or more. Both cannabis use and the prevalence of symptoms of anxiety and depression were found to increase with age. Girls reported less use of cannabis and slightly more symptoms of anxiety and depression compared to boys. Conclusions: The present study contributes to the existing knowledge about important associations between cannabis use and symptoms of anxiety and depression in adolescents. Future research should focus on longitudinal methods in order to better understand the role of environmental and neurobiological explanatory factors.

Kamal, B. S., F. Kamal, et al. (2018). "Cannabis and the Anxiety of Fragmentation—A Systems Approach for Finding an Anxiolytic Cannabis Chemotype." Frontiers in Neuroscience **12**(730).

Cannabis sativa is a medicinal herb with a diverse range of chemotypes that can exert both anxiolytic and anxiogenic effects on humans. Medical cannabis patients receiving organically grown cannabis from a single source were surveyed about the effectiveness of cannabis for treating anxiety. Patients rated cannabis as highly effective overall for treating anxiety with an average score of 8.03 on a Likert scale of 0 to 10 (0=not effective,10=extremely effective). Patients also identified which strains they found the most or least effective for relieving their symptoms of anxiety. To find correlations between anxiolytic activity and chemotype, the top four strains voted most and least effective were analyzed by HPLC-MS/MS to quantify cannabinoids and GC-MS to quantify terpenes. Tetrahydrocannabinol and trans-nerolidol have statistically significant correlations with increased anxiolytic activity. Guiaol, eucalyptol, γ-terpinene, α-phellandrene, 3-carene and sabinene hydrate all have significant correlations with decreased anxiolytic activity. Further studies are needed to better elucidate the entourage effects that contribute to the anxiolytic properties of cannabis varieties.

Kanaan, A. S. and K. R. Müller-Vahl (2017). Chapter 92 - Cannabinoid-Based Medicines for the Treatment of Gilles de la Tourette Syndrome A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 883-892.

Abstract Gilles de la Tourette syndrome (GTS) is a common psychiatric movement disorder that is characterized by motor and vocal tics and a strong association with comorbid obsessive compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD). On a systems level, the primary abnormality has been shown to be related to dopaminergic neurotransmission within cortico-striato-thalamo-cortical (CSTC) circuits, though a complete picture of the disorder’s pathophysiology remains elusive. Clinically, the therapeutic spectrum for GTS has been expanding over the last decade, though current treatment strategies are often ineffective and unsatisfactory. As a result, there is an urgent need for uncovering novel treatment strategies that could ameliorate both motor and behavioral symptoms, are more effective in treatment resistant patients, and cause less adverse effects. Early anecdotal reports have provided evidence that patients with GTS choose cannabinoids as a form of self-medication. As a result, several groups began investigating the role of the endocannabinoid system in GTS pathophysiology and cannabinoid based medicines as a form of treatment. Currently, there are a limited number of studies suggesting that oral Δ9-tetrahydrocannabinol (THC) is effective in the treatment of tics and behavioral comorbidities. Consequently, the role of the endocannabinoid system in GTS pathophysiology remains speculative, as further investigation on the role of the endocannabinoid system in GTS is needed. In this chapter, we review the state of the art and highlight studies that explored the role of the endocannabinoid system and cannabinoids based medicine in GTS.

Kansagara, D., W. C. Becker, et al. (2019). "Priming primary care providers to engage in evidence-based discussions about cannabis with patients." Addiction Science & Clinical Practice **14**(1): 42.

Cannabis use has become increasingly common in the U.S. in recent years, with legalization for medical and recreational purposes expanding to more states. With this increase in use and access, providers should be prepared to have more conversations with patients about use. This review provides an overview of cannabis terminology, pharmacology, benefits, harms, and risk mitigation strategies to help providers engage in these discussions with their patients. Current evidence for the medical use of cannabis, cannabis-related diagnoses including cannabis use disorder (CUD) and withdrawal syndromes, and the co-use of opioids and cannabis are discussed. It is crucial that providers have the tools and information they need to deliver consistent, evidence-based assessment, treatment, prevention and harm-reduction, and we offer practical guidance in these areas.

Kansagara, D., B. J. Morasco, et al. (2020). "Clinician Knowledge, Attitudes, and Practice Regarding Cannabis: Results from a National Veterans Health Administration Survey." Pain Med.

BACKGROUND: Cannabis is increasingly available and used for medical and recreational purposes, but few studies have assessed provider knowledge, attitudes, and practice regarding cannabis. METHODS: We administered a 47-item electronic survey to assess nationwide Veterans Health Administration (VHA) clinician knowledge, beliefs, attitudes, and practice regarding patients' use of cannabis. RESULTS: We received 249 completed surveys from 39 states and the District of Columbia. Fifty-five percent of respondents were female, 74% were white, and the mean age was 50 years. There were knowledge gaps among a substantial minority of respondents in specific areas: terminology, psychoactive effects of cannabis components, VHA policy, and evidence regarding benefits and harms of cannabis. Most respondents were likely or very likely to plan to taper opioids if urine drug testing was positive for tetra-hydro cannabinol (THC; 73%). A significantly greater proportion of respondents from states in which cannabis is illegal for any purpose (odds ratio [OR] = 4.9, 95% confidence interval [CI] = 2.0-10.8) or is recreationally illegal (OR = 5.0, 95% CI = 2.4-10.8) reported being likely or very likely to taper opioids as compared with respondents from states in which cannabis is legal for medical and recreational purposes. CONCLUSIONS: Among the sample, we found knowledge gaps, areas of discomfort discussing key aspects of cannabis use with their patients, and variation in practice regarding opioids in patients also using THC. These results suggest a need for more widespread clinician education about cannabis, as well as an opportunity to develop more robust guidance and evidence regarding management of patients using prescription opioids and cannabis concomitantly.

Karanges, E. A., A. Suraev, et al. (2018). "Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey." BMJ Open 8(7).

Objectives: To examine the knowledge and attitudes of Australian general practitioners (GP) towards medicinal cannabis, including patient demand, GP perceptions of therapeutic effects and potential harms, perceived knowledge and willingness to prescribe. Design, setting and participants: A cross-sectional survey completed by 640 GPs (response rate=37%) attending multiple-topic educational seminars in five major Australian cities between August and November 2017.Main outcome measures: Number of patients enquiring about medicinal cannabis, perceived knowledge of GPs, conditions where GPs perceived it to be beneficial, willingness to prescribe, preferred models of access, perceived adverse effects and safety relative to other prescription drugs. Results: The majority of GPs (61.5%) reported one or more patient enquiries about medicinal cannabis in the last three months. Most felt that their own knowledge was inadequate and only 28.8% felt comfortable discussing medicinal cannabis with patients. Over half (56.5%) supported availability on prescription, with the preferred access model involving trained GPs prescribing independently of specialists. Support for use of medicinal cannabis was condition-specific, with strong support for use in cancer pain, palliative care and epilepsy, and much lower support for use in depression and anxiety. Conclusions: The majority of GPs are supportive or neutral with regards to medicinal cannabis use. Our results highlight the need for improved training of GPs around medicinal cannabis, and the discrepancy between GP-preferred models of access and the current specialist-led models.

Karim, S., W. Y. Cheung, et al. (2020). "Medical Cannabis Authorization in Patients With Cancer in the Prelegalization Era: A Population-Based Study." J Pain Symptom Manage **59**(6): 1223-1231.

CONTEXT: Studies show that patients with cancer use cannabis to manage symptoms and side effects. Medical cannabis is regulated by Health Canada; authorization patterns among cancer patients have not been well described. OBJECTIVES: The aim of the study is to describe medical cannabis authorization in Alberta, Canada. METHODS: The Alberta Cancer Registry was used to identify all patients aged 18 years and older diagnosed with invasive cancer from April 1, 2014 to December 31, 2016. These cases were linked to records from the College of Physicians and Surgeons of Alberta. Univariate and multivariate logistic regression models were constructed to determine factors associated with medical cannabis authorization. RESULTS: We identified 41,889 patients with cancer between April 1, 2014 and December 31, 2016. Of these patients, 1070 (2.6%) had a medical cannabis authorization. Fifty-one percent (541 of 1070) were authorized to use medical cannabis within one year of diagnosis, 52% (248 of 549) within one year of the start of systemic therapy, and 41% (128 of 312) within one year of the start of radiation therapy. Patients aged 18-29 (odds ratio [OR] 12.4; 95% CI 7.8-19.8), patients living in the Calgary zone (OR 1.8; 95% CI 1.6-2.1), those with advanced disease (Stage III/IV: OR 1.2; 95% CI 1.0-1.4), and those receiving systemic therapy (OR 2.0; 95% CI 1.7-2.4) were more likely to have an authorization for medical cannabis (P < 0.001). CONCLUSION: A small proportion of patients with cancer were authorized to use medical cannabis between 2014 and 2016 in Alberta. Authorization was associated with a cancer diagnosis and receiving treatment. Younger patients, those with advanced stage disease, and those undergoing systemic treatment were predictors of medical cannabis authorization.

Karst, A. (2018). Weighing the Benefits and Risks of Medical Marijuana Use: A Brief Review.

Despite federal prohibition of medical marijuana possession, sale, and use, marijuana use continues to escalate as state legalization persists and expands. The purpose of this discussion is to provide a brief summary of the evidence regarding both potential benefits and risks of medical marijuana use.

Katz-Talmor, D., I. Katz, et al. (2018). Cannabinoids for the treatment of rheumatic diseases — where do we stand? Nature Reviews Rheumatology. **14:** 1.

As medical use of cannabis is increasingly legalized worldwide, a better understanding of the medical and hazardous effects of this drug is imperative. The pain associated with rheumatic diseases is considered a prevalent indication for medicinal cannabis in various countries. Thus far, preliminary clinical trials have explored the effects of cannabis on rheumatoid arthritis, osteoarthritis and fibromyalgia; preliminary evidence has also found an association between the cannabinoid system and other rheumatic conditions, including systemic sclerosis and juvenile idiopathic arthritis. The potential medicinal effects of cannabis could be attributable to its influence on the immune system, as it exerts an immunomodulatory effect on various immune cells, including T cells, B cells and macrophages. However, the available evidence is not yet sufficient to support the recommendation of cannabinoid treatment for rheumatic diseases.

Keles, H. O., M. Radoman, et al. (2017). "Using Functional Near-Infrared Spectroscopy to Measure Effects of Delta 9-Tetrahydrocannabinol on Prefrontal Activity and Working Memory in Cannabis Users." Frontiers in Human Neuroscience **11**(488).

Intoxication from cannabis impairs cognitive performance, in part due to the effects of Δ9-tetrahydrocannabinol (THC, the primary psychoactive compound in cannabis) on prefrontal cortex (PFC) function. However, a relationship between impairment in cognitive functioning with THC administration and THC-induced change in hemodynamic response has not been demonstrated. We explored the feasibility of using functional near-infrared spectroscopy (fNIRS) to examine the functional changes of the human PFC associated with cannabis intoxication and cognitive impairment. Eighteen adult regular cannabis users (final sample, n = 13) performed a working memory task (n-back) during fNIRS recordings, before and after receiving a single dose of oral synthetic THC (dronabinol; 20-50mg). Functional data were collected using a continuous-wave NIRS device, in which 8 Sources and 7 detectors were placed on the forehead, resulting in 20 channels covering PFC regions. Physiological changes and subjective intoxication measures were collected. We found a significant increase in the oxygenated hemoglobin (HbO) concentration after THC administration in several channels on the PFC during both the high working memory load (2-back) and the low working memory load (0-back) condition. The increased HbO response was accompanied by a trend towards an increased number of omission errors after THC administration. The current study suggests that cannabis intoxication is associated with increases in hemodynamic blood flow to the PFC, and that this increase can be detected with fNIRS.

Kerlin, A. M., M. Long, et al. (2018). "Profiles of Patients Who Use Marijuana for Inflammatory Bowel Disease." Dig Dis Sci **63**(6): 1600-1604.

BACKGROUND: Marijuana is legal in a number of states for indications that include inflammatory bowel diseases (IBD), and patients are interested in its potential benefits. AIMS: We aimed to describe the legal use of marijuana in individuals with IBD in the USA who participate within the CCFA Partners internet-based cohort. METHODS: A total of 2357 participants who lived in states where prescription or recreational marijuana was legal, were offered the opportunity to complete a survey on marijuana use and IBD symptoms including perceived benefits of therapy. Bivariate statistics and logistic regression models were used to determine factors associated with marijuana use. RESULTS: Surveys were completed by 1666 participants (71%) with only 214 (12.8%) indicating they had asked their medical doctor about its use and 73 actually using prescribed marijuana (4.4%). Within the respondent group (N = 1666), 234 participants lived where both medical and recreational marijuana is legal and 49 (20.9%) reported recreational marijuana use specifically for IBD. Users reported positive benefits (80.7%), but users also reported more depression, anxiety, pain interference, and lower social satisfaction than non-users. Those prescribed marijuana reported more active disease, and more use of steroids, narcotics, and zolpidem. CONCLUSIONS: Few IBD patients consulted their medical doctors about marijuana use or used prescription marijuana. Where recreational marijuana was available, usage rates were higher. Users reported benefits but also more IBD symptoms, depression, anxiety, and pain. Marijuana use may be higher in patients with IBD symptoms not well treated by conventional medical approaches.

Keresztes, A. and J. M. Streicher (2017). "Synergistic interaction of the cannabinoid and death receptor systems – a potential target for future cancer therapies?" FEBS Letters **591**(20): 3235-3251.

Cannabinoid receptors have been shown to interact with other receptors, including tumor necrosis factor receptor superfamily (TNFRS) members, to induce cancer cell death. When cannabinoids and death-inducing ligands (including TNF-related apoptosis-inducing ligand) are administered together, they have been shown to synergize and demonstrate enhanced antitumor activity in vitro. Certain cannabinoid ligands have been shown to sensitize cancer cells and synergistically interact with members of the TNFRS, thus suggesting that the combination of cannabinoids with death receptor (DR) ligands induces additive or synergistic tumor cell death. This review summarizes recent findings on the interaction of the cannabinoid and DR systems and suggests possible clinical co-application of cannabinoids and DR ligands in the treatment of various malignancies.

Kerrie-Anne Chen, M. A. F., Michael Cardamone and John A Lawson (2018). "Cannabis for paediatric epilepsy: challenges and conundrums." Med J Aust 2018 **208**(3): 132 - 136.

Research is expanding for the use of cannabidiol as an anticonvulsant drug. The mechanism of cannabidiol in paediatric epilepsy is unclear but is thought to play a role in modulation of synaptic transmission. Evidence for its efficacy in treating epilepsy is limited but growing, with a single pharmaceutical company-funded randomised double-blind controlled trial in children with Dravet syndrome. Progress towards the use of medicinal cannabinoids incorporates a complex interplay of social influences and political and legal reform. Access to unregistered but available cannabidiol in Australia outside of clinical trials and compassionate access schemes is state dependent and will require Therapeutic Goods Administration approval, although the cost may be prohibitive. Further clinical trials are needed to clearly define efficacy and safety, particularly long term.

Khadanga, S. and P. A. Ades (2018). "What do we tell patients with coronary artery disease about marijuana use?" Coronary Artery Disease **29**(1): 1-3.

As of 2017, seven states and the District of Columbia have legalized the recreational use of marijuana, with almost certainly more to follow. Cardiovascular physicians will need to address whether this use might be harmful to patients with cardiovascular disease, particularly coronary heart disease (CHD). Marijuana use is an increasing phenomenon with 9.5% of the US adults admitting to the use of marijuana in 2012–2013 versus 4.1% in 2001–2002 1. Furthermore, in 2014, 2.5 million people in the USA aged older than or equal to 12 years used marijuana for the first time during the preceding 12 months, resulting in an average of ~7000 new users each day 2. The manifestations of increased marijuana use have specific implications in cardiac care. A relative paucity of research exists that establishes links between marijuana use and total mortality for those affected by CHD. One study showed that over a median follow-up of 3.8 years, there was a three-fold increased risk of mortality following acute myocardial infarction (MI) in patients with CHD after marijuana use, after adjusting for smoking status and socioeconomic status, with a graded increase in risk (i.e. a dose–response) with more frequent use 3. This study analyzed self-reported use of marijuana in the preceding year. Furthermore, smoking marijuana has been implicated as a trigger for inducing MI with the risk of MI onset being elevated almost five-fold in the hour after smoking 4. However, long-term results for marijuana use are somewhat mixed as one study in patients with CHD with a follow-up of 18 years found no statistically significant association between marijuana use and total mortality, although mortality rate was 29% higher (P=0.28) among those reporting any marijuana use 5. Though the long-term effects of marijuana use are less clear, all three of these studies paint a negative picture for marijuana use in coronary artery disease patients by indicating an elevated risk of increase in MI and/or mortality. With rates of marijuana use in the USA clearly increasing, this area is ripe for further research.

Khan, R., S. Naveed, et al. (2020). "The therapeutic role of Cannabidiol in mental health: a systematic review." Journal of Cannabis Research **2**(1): 2.

Abstract

Background

The therapeutic application of cannabidiol (CBD) is gaining interest due to expanding evidence for its use.

Objective

To summarize the clinical outcomes, study designs and limitations for the use of CBD and nabiximols (whole plant extract from Cannabis sativa L. that has been purified into 1:1 ratio of CBD and delta-9-tetrahydrocannabinol) in the treatment of psychiatric disorders.

Materials and method

A systematic review was conducted including case reports, case series, open-label trials, non-randomized and randomized controlled trials (RCTs). The search resulted in 23 relevant studies on CBD and nabiximols in the treatment of a wide range of psychiatric disorders. The quality of evidence was judged by using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence that ranges from Level 1 to Level 5 based on the quality and study design. These levels of evidence help in grading the recommendations, including Grade A (strong), Grade B (moderate), Grade C (weak), and Grade D (weakest).

Results

CBD and CBD-containing compounds such as nabiximols were helpful in alleviating psychotic symptoms and cognitive impairment in patients with a variety of conditions, and several studies provided evidence of effectiveness in the treatment of cannabis withdrawal and moderate to severe cannabis use disorder with Grade B recommendation. There is Grade B recommendation supporting the use of CBD for the treatment of schizophrenia, social anxiety disorder and autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). Grade C recommendation exists for insomnia, anxiety, bipolar disorder, posttraumatic stress disorder, and Tourette syndrome. These recommendations should be considered in the context of limited number of available studies.

Conclusion

CBD and CBD-containing compounds such as nabiximols were helpful in alleviating symptoms of cannabis-related disorders, schizophrenia, social anxiety disorder, and comorbidities of ASD, and ADHD with moderate recommendation. However, there is weaker evidence for insomnia, anxiety, bipolar disorder, posttraumatic stress disorder, and Tourette syndrome. The evidence for the use of CBD and CBD-containing compounds for psychiatric disorders needs to be explored in future studies, especially large-scale and well-designed RCTs

Kiefer, D. (2017). Topical cannabis for wound pain: A case series.

For three people with continued pain despite conventional treatment for pyoderma gangrenosum, topical cannabis led to statistically significant pain relief for two of them.

Kienzl, M., M. Storr, et al. (2020). "Cannabinoids and Opioids in the Treatment of Inflammatory Bowel Diseases." Clin Transl Gastroenterol **11**(1): e00120.

In traditional medicine, Cannabis sativa has been prescribed for a variety of diseases. Today, the plant is largely known for its recreational purpose, but it may find a way back to what it was originally known for: a herbal remedy. Most of the plant's ingredients, such as Delta-tetrahydrocannabinol, cannabidiol, cannabigerol, and others, have demonstrated beneficial effects in preclinical models of intestinal inflammation. Endogenous cannabinoids (endocannabinoids) have shown a regulatory role in inflammation and mucosal permeability of the gastrointestinal tract where they likely interact with the gut microbiome. Anecdotal reports suggest that in humans, Cannabis exerts antinociceptive, anti-inflammatory, and antidiarrheal properties. Despite these reports, strong evidence on beneficial effects of Cannabis in human gastrointestinal diseases is lacking. Clinical trials with Cannabis in patients suffering from inflammatory bowel disease (IBD) have shown improvement in quality of life but failed to provide evidence for a reduction of inflammation markers. Within the endogenous opioid system, mu opioid receptors may be involved in anti-inflammation of the gut. Opioids are frequently used to treat abdominal pain in IBD; however, heavy opioid use in IBD is associated with opioid dependency and higher mortality. This review highlights latest advances in the potential treatment of IBD using Cannabis/cannabinoids or opioids.

Kim, S. H., J. W. Yang, et al. (2019). "A Review on Studies of Marijuana for Alzheimer's Disease - Focusing on CBD, THC." Journal of pharmacopuncture **22**(4): 225-230.

OBJECTIVES: This study was to discuss the research trend of dementia treatment using cannabis for the purpose of providing the basis of cannabis use for medical purposes in the future. METHODS: This study searched publications, which were registered to databases or published by Aug 22, 2019, and targeted the full-text or abstracts of these publications. We selected the final nine studies met all selection criteria. RESULTS: These results implied that the CBD components of cannabis might be useful to treat and prevent AD because CBD components could suppress the main causal factors of AD. Moreover, it was suggested that using CBD and THC together could be more useful than using CBD or THC alone. CONCLUSION: We hope that there will be a solid foundation to use cannabis for medical use by continuously evaluating the possibility of using cannabis for clinical purposes as a dementia treatment substance and cannabis can be used as a positive tool.

Klein, M., J. De Quadros De Bortolli, et al. (2020). "EFFECTS OF CANNABIDIOL, A CANNABIS SATIVA CONSTITUENT, ON ORAL WOUND HEALING." Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 129(1): e166-e167.

Objective To evaluate the effect of cannabidiol (CBD) on the healing of rats’ oral wounds. Study Design Traumatic ulcers were induced in 60 Wistar rats using a 5-mm biopsy punch on the midline of the ventral tongue. Animals received daily intraperitoneal (ip) injections of CBD at doses of 0 (control), 5 or 10 mg/kg. Rats were weighed daily and sacrificed after 3 and 7 days of treatment. Clinical (ulcer area and weight variation) and histopathologic (inflammation scores) analyses were performed. Data were analyzed statistically at the significance level of 5%. Results CBD was unable to clinically influence the size of ulcerative lesions. However, treatment with CBD in both tested concentrations decreased inflammatory scores after 3 days post-wounding (P < .05) compared to control. Conclusions Five and 10 mg/kg CBD exerted promising anti-inflammatory effect in oral ulcerative lesions, not being enough to accelerate clinical wound healing at 3 and 7 days.

Klotz, K. A., D. Grob, et al. (2019). "Efficacy and Tolerance of Synthetic Cannabidiol for Treatment of Drug Resistant Epilepsy." Frontiers in Neurology 10: 1313.

Objective: Controlled and open label trials have demonstrated efficacy of cannabidiol for certain epileptic encephalopathies. However, plant derived cannabidiol products have been used almost exclusively. Efficacy of synthetically derived cannabidiol has not been studied before. The objective of this study was to evaluate tolerability and efficacy of synthetic cannabidiol in patients with pharmacoresistant epilepsy.Methods: In this prospective, open-label study (DRKS00013177), patients with pharmacoresistant epilepsy received synthetic cannabidiol in addition to their previously stable anticonvulsive treatment. Starting dose was 5 mg/kg/day, up-titrated to a maximum of 50 mg/kg/day. Primary efficacy endpoint was monthly frequency of motor seizures at 3 months.Results: Between April 2017 and May 2019, 35 patients were enrolled in the study. Mean age was 19.7 years (SD 14.6). Median motor seizure frequency decreased from 21.8 (IQR 7.5–52.5) seizures per month at baseline to 8.5 (IQR 3.7–28.3, p < 0.001) at 3 months, effect not influenced by AED changes and drop-outs. Adjusted percentage reduction was 40.0% (IQR 18.2–58.5). Adverse events (AE) were reported in 25 patients (71.4%), most frequently somnolence (40%), diarrhea (34.3), and loss of appetite (20%). Two patients (5.7%) discontinued treatment due to AE. Median (range) of treatment duration was 321 days (range 36–824). With ongoing treatment up to date in 21 patients (60%).Conclusion: Efficacy and tolerance in our study of synthetic CBD treatment in pharmacoresistant epilepsy is similar to open label studies using plant derived CBD. Regarding economic and ecological aspects, synthetic cannabidiol might be a reasonable alternative to plant derived cannabidiol.

Kortubash, I., C. Skinner, et al. (2020). "Cannabidiol: From Drug Interaction Potential to Modulation of the Gut Microbiome." Current Developments in Nutrition **4**(Supplement\_2): 418-418.

Cannabidiol (CBD) is the major non-psychotropic phytocannabinoid present in Cannabis sativa. In 2018, Congress designated select C. sativa cultivars as “hemp” removing them from the DEA's list of controlled substances. As a result, CBD-containing hemp extracts and other CBD products are now widely available and heavily marketed, yet their FDA regulatory status is still hotly debated. Further complicating the debate is CBD's vastly under-researched safety profile. Safety concerns yet to be adequately addressed include CBD's drug interaction potential and its effect on the gut microbiome.Using acetaminophen (APAP), the most commonly ingested over-the-counter pain medication, we demonstrated that CBD-rich cannabis extract (CRCE) poses a significant drug interaction risk.Mice exposed to both CRCE and APAP developed severe liver injury. This hepatotoxicity, however, was not observed when either CRCE or APAP were administered separately. Importantly, this injury was observed in two different strains of mice with susceptibilities seemingly linked to sex (female) and age (older animals). Furthermore, both beneficial and adverse effects of CRCE on the gut microbiome were observed. Specifically, CRCE exposure increased the relative abundance of the beneficial gut microbe, Akkermansia muciniphila, however, an overall decrease in the relative abundance of all gut bacterial species was noted. This decrease was paralleled by numerous pro-inflammatory responses in the proximal jejunum and colon.Taken together, these findings raise significant concerns about the safety of widespread CBD usage and underlines the need for additional well-designed studies into its safety and efficacy.NIGMS 1P20 GM109005.

Kosiba, J. D., S. A. Maisto, et al. (2019). "Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis." Soc Sci Med 233: 181-192.

RATIONALE: Certifications for medical cannabis are generally restricted to a small number of specific medical conditions, yet patients frequently report symptoms of pain, anxiety, and depression as reasons for use. This is a critical concern for researchers, healthcare providers, and policymakers, yet research in this area is currently obstructed by the lack of a focused review or empirical synthesis on patient-reported reasons for medical cannabis use. OBJECTIVES: AND METHOD: The first aim of this project was to conduct the first systematic review and meta-analysis of empirical studies of patient-reported symptoms of pain, anxiety, and depression as reasons for medical cannabis use. The second aim was to conduct an empirical assessment of the methodological quality of extant research, test for publication bias, and test sex composition and quality scores of individual studies as possible sources of observed heterogeneity. RESULTS: Meta-analytic results indicated that pain (64%), anxiety (50%), and depression/mood (34%) were common reasons for medical cannabis use. No evidence for publication bias was detected, despite heterogeneity in prevalence rates. A comprehensive assessment of study quality identified a number of specific methodological limitations of the existing research, including challenges in patient recruitment, use of restrictive sampling frames, and a lack of randomized recruitment methods and validated assessment measures. CONCLUSION: Findings are discussed with regard to possible explanations for current results, clinical considerations, and areas of future research that are needed to move the field forward.

Kosiba, J. D., L. D. Mitzel, et al. (2020). "A preliminary study of associations between discomfort intolerance, pain severity/interference, and frequency of cannabis use among individuals with chronic pain." Addiction Research & Theory **28**(1): 76-81.

AbstractBackground: Cannabis use is more common among individuals with chronic pain, and is often used to relieve physical discomfort. However, little is known about factors that are associated with cannabis use among individuals with chronic pain, and there is reason to suspect that perceptions of discomfort intolerance (DI) play an important role in pain-cannabis relations. Method: The goal of this study was to conduct an initial examination of perceived DI, pain severity, and pain-related interference in relation to frequency of cannabis use among individuals with chronic pain. Specifically, we hypothesized that pain severity/interference and factors of DI (avoidance and intolerance), would each be positively associated with cannabis use frequency. Results: Participants (N?=?109; 44% male; Mage?=?27) endorsed chronic pain and at least one instance of lifetime cannabis use. Most participants characterized their chronic pain as high intensity and low disability, and the two most commonly reported frequencies of cannabis use were ?less than monthly? (n?=?38), and ?daily/almost daily? (n?=?32). Results indicated that discomfort avoidance (but not discomfort intolerance), pain severity, and pain-related interference were each independently and positively associated with frequency of cannabis use.Conclusions: These preliminary findings suggest that continued examination of perceived discomfort avoidance in relation to co-occurring pain and cannabis use is warranted. Future research should replicate these results among treatment-seeking pain patients who are prescribed medical cannabis.

Koubeissi, M. (2017). "Anticonvulsant Effects of Cannabidiol in Dravet Syndrome." Epilepsy Currents **17**(5): 281-282.

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. We studied cannabidiol for the treatment of drug-resistant seizures in the Dravet syndrome. METHODS: In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. RESULTS: The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% confidence interval [CI], −41.1 to −5.4; P=0.01). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group (P=0.02). The frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo (P=0.08). Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group. CONCLUSIONS: Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. (Funded by GW Pharmaceuticals; ClinicalTrials.gov number, NCT02091375).

Krediet, E., D. G. A. Janssen, et al. (2020). "Experiences with medical cannabis in the treatment of veterans with PTSD: Results from a focus group discussion." European Neuropsychopharmacology **36**: 244-254.

Posttraumatic stress disorder (PTSD) is an often chronic condition for which currently available medications have limited efficacy. Medical cannabis is increasingly used to treat patients with PTSD; however, evidence for the efficacy and safety of cannabinoids is scarce. To learn more about patients' opinions on and experiences with medical cannabis, we organized a focus group discussion among military veterans (N = 7) with chronic PTSD who were treated with medical cannabis. Afterwards, some of their partners (N = 4) joined the group for an evaluation, during which they shared their perspective on their partner's use of medical cannabis. Both sessions were audio-recorded, transcribed verbatim, and analyzed by means of qualitative content analysis. Five overarching themes were identified. The first four themes related to the different phases of medical cannabis use – namely, 1) Consideration; 2) Initiation; 3) Usage; and 4) Discontinuation. The fifth theme related to several general aspects of medical cannabis use. Patients used medical cannabis to manage their symptoms and did not experience an urge to “get high.” They used a variety of different cannabis strains and dosages and reported several therapeutic effects, including an increased quality of sleep. Furthermore, discussions about the experienced stigma surrounding cannabis generated insights with implications for the initiation of medical cannabis use. These results underscore the value of qualitative research in this field and are relevant for the design of future clinical trials on the use of medical cannabis for the treatment of PTSD.

Kruger, D. J., J. S. Kruger, et al. (2020). "Cannabis Enthusiasts' Knowledge of Medical Treatment Effectiveness and Increased Risks From Cannabis Use." Am J Health Promot **34**(4): 436-439.

PURPOSE: To compare cannabis enthusiasts' knowledge about cannabis risks and effectiveness in treating medical conditions with existing empirical evidence. DESIGN: A brief survey assessed cannabis use, information sources, and knowledge about risks and effectiveness. SETTING: A cannabis advocacy event in April 2019 in a state with legal medical and recreational cannabis. PARTICIPANTS: Demographically diverse adults (N = 472) who frequently used cannabis; 85% used cannabis for health or medical purposes. MEASURES: Participants reported the sources of their cannabis information, health conditions they thought cannabis was effective in treating (n = 10), and health risks increased by cannabis (n = 6). Conditions and risks were based on ratings of evidence (ie, from substantial to insufficient) for therapeutic effects and risks identified in a review by The National Academies of Sciences, Engineering, and Medicine (NASEM, 2017). ANALYSES: Chi-square tests examined the correspondence between participants' knowledge and NASEM conclusions. RESULTS: Most participants' (95% confidence interval [CI]: 74%-81%) knowledge of cannabis was from their own experiences; 18% (95% CI: 14%-21%) received information from primary care providers. On average, participants' beliefs matched NASEM conclusions for half of effectiveness (95% CI: 50%-53%) and risk items (95% CI: 55%-57%). Many (95% CI: 38%-42%) thought that cannabis use did not increase any risk. Contrary to NASEM conclusions, many thought cannabis was effective in treating cancer (76%), depressive symptoms (72%), and epilepsy (68%). Those who received cannabis information from their primary care providers had better knowledge of medical effectiveness. Medicinal cannabis use frequency inversely predicted knowledge of medical effectiveness and increased risks of adverse events. CONCLUSION: There were considerable discrepancies between cannabis users' knowledge and available evidence, highlighting the need for more research and education (by physicians, caregivers, and dispensaries) on effectiveness and health risks, especially for users with specific health issues such as pregnant women and people with depression.

Lac, A. and J. W. Luk (2018). "Testing the Amotivational Syndrome: Marijuana Use Longitudinally Predicts Lower Self-Efficacy Even After Controlling for Demographics, Personality, and Alcohol and Cigarette Use." Prevention Science **19**(2): 117-126.

The marijuana amotivational syndrome posits that cannabis use fosters apathy through the depletion of motivation-based constructs such as self-efficacy. The current study pursued a two-round design to rule out concomitant risk factors responsible for the connection from marijuana intake to lower general self-efficacy. College students (N = 505) completed measures of marijuana use, demographics (age, gender, and race), personality (extraversion, agreeableness, conscientiousness, openness, and neuroticism), other substance use (alcohol and tobacco), and general self-efficacy (initiative, effort, and persistence) in two assessments separated by a month. Hierarchical regression models found that marijuana use forecasted lower initiative and persistence, even after statistically ruling out 13 pertinent baseline covariates including demographics, personality traits, alcohol use, tobacco use, and self-efficacy subscales. A cross-lagged panel model involving initiative, effort, persistence, alcohol use, cigarette use, and marijuana use sought to unravel the temporal precedence of processes. Results showed that only marijuana (but not alcohol or tobacco) intake significantly and longitudinally prompted lower initiative and persistence. Furthermore, in the same model, the opposite temporal direction of events from lower general self-efficacy subscales to marijuana use was untenable. Findings provide partial support for the marijuana amotivational syndrome, underscore marijuana as a risk factor for decreased general self-efficacy, and offer implications and insights for marijuana prevention and future research.

LaFrance, E. M., N. C. Glodosky, et al. (2020). "Short and Long-Term Effects of Cannabis on Symptoms of Post-Traumatic Stress Disorder." Journal of Affective Disorders **274**: 298-304.

Background Many individuals use cannabis to manage symptoms of post-traumatic stress disorder (PTSD), and evidence indicates that the endocannabinoid system represents a viable target for treating these symptoms. Method Data from 404 medical cannabis users who self-identified as having PTSD were obtained from Strainprint®, a medical cannabis app that patients use to track changes in symptoms as a function of different strains and doses of cannabis across time. This sample collectively used the app 11,797 times over 31 months to track PTSD-related symptoms (intrusive thoughts, flashbacks, irritability, and/or anxiety) immediately before and after inhaling cannabis. Latent change score models were used to examine changes in symptom severity and predictors of these changes (gender, dose, cannabis constituents, time). Multilevel models were used to explore long-term consequences of repeatedly using cannabis to manage these symptoms. Results All symptoms were reduced by more than 50% immediately after cannabis use. Time predicted larger decreases in intrusions and irritability, with later cannabis use sessions predicting greater symptom relief than earlier sessions. Higher doses of cannabis predicted larger reductions in intrusions and anxiety, and dose used to treat anxiety increased over time. Baseline severity of all symptoms remained constant across time. Limitations The sample was self-selected, self-identified as having PTSD, and there was no placebo control group. Conclusions Cannabis provides temporary relief from PTSD-related symptoms. However, it may not be an effective long-term remedy as baseline symptoms were maintained over time and dose used for anxiety increased over time, which is indicative of development of tolerance.

Lahat, A. (2017). Chapter 96 - Medical Cannabis for the Treatment of Inflammatory Bowel Disease A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 931-938.

Abstract The beneficial effect of cannabinoids on the gastrointestinal (GI) tract has been recognized for centuries. However, until recently, little attention was attributed toward the medical usage of cannabis in patients suffering from inflammatory bowel disease (IBD). In the past years, a few clinical studies approaching this subject were published. Summarizing all the published results leads to the conclusion that cannabis can be beneficial for IBD symptoms relief. Patients reported significant improvement in abdominal pain, diarrhea, increased appetite, and improved quality of life. Side effects, if any, were mild. However, these were small studies, and only one of them was double-blind placebo controlled. Therefore, more double-blind placebo-controlled large volume studies are warranted in order to assess the utility, indications, and contraindications to cannabis use as a therapeutic tool in IBD patients.

Lake, S., T. Kerr, et al. (2020). "Does cannabis use modify the effect of post-traumatic stress disorder on severe depression and suicidal ideation? Evidence from a population-based cross-sectional study of Canadians." J Psychopharmacol **34**(2): 181-188.

BACKGROUND: Post-traumatic stress disorder sharply increases the risk of depression and suicide. Individuals living with post-traumatic stress disorder frequently use cannabis to treat associated symptoms. We sought to investigate whether cannabis use modifies the association between post-traumatic stress disorder and experiencing a major depressive episode or suicidal ideation. METHODS: We used data from the 2012 Canadian Community Health Survey-Mental Health, a nationally representative cross-sectional survey of non-institutionalized Canadians aged ⩾15 years. The relationship between post-traumatic stress disorder and each outcome was modelled using logistic regression with an interaction term for cannabis and post-traumatic stress disorder, controlling for demographic characteristics, mental health, and substance use comorbidities. The ratio of odds ratios and relative excess risk due to interaction was calculated to measure interaction on the multiplicative and additive scales, respectively. RESULTS: Among 24,089 eligible respondents, 420 (1.7%) reported a current clinical diagnosis of post-traumatic stress disorder. In total, 106 (28.2%) people with post-traumatic stress disorder reported past-year cannabis use, compared to 11.2% of those without post-traumatic stress disorder (p < 0.001). In multivariable analyses, post-traumatic stress disorder was significantly associated with recent major depressive episode (adjusted odds ratio = 7.18, 95% confidence interval: 4.32-11.91) and suicidal ideation (adjusted odds ratio = 4.76, 95% confidence interval: 2.39-9.47) among cannabis non-users. post-traumatic stress disorder was not associated with either outcome among cannabis-using respondents (both p > 0.05). CONCLUSIONS: This study provides preliminary epidemiological evidence that cannabis use may contribute to reducing the association between post-traumatic stress disorder and severe depressive and suicidal states. There is an emerging need for high-quality experimental investigation of the efficacy of cannabis/cannabinoids for the treatment of post-traumatic stress disorder.

Landa, L., J. Jurica, et al. (2018). "Medical cannabis in the treatment of cancer pain and spastic conditions and options of drug delivery in clinical practice." Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 162(1): 18-25.

The use of cannabis for medical purposes has been recently legalised in many countries including the Czech Republic. As a result, there is increased interest on the part of physicians and patients in many aspects of its application. This mini review briefly covers the main active substances of the cannabis plant and mechanisms of action. It focuses on two conditions, cancer pain and spasticity in multiple sclerosis, where its effects are well-documented. A comprehensive overview of a few cannabis-based products and the basic pharmacokinetics of marijuana's constituents follows. The review concludes with an outline for preparing cannabis (dried inflorescence) containing drug dosage forms that can be produced in a hospital pharmacy.

Lankenau, S. E., J. Ataiants, et al. (2018). "Health conditions and motivations for marijuana use among young adult medical marijuana patients and non-patient marijuana users." Drug and Alcohol Review **37**(2): 237-246.

Introduction: While marijuana has been legal for medical purposes in California since 1996, little is known about the health histories of young adult medical marijuana patients who are a significant proportion of medical marijuana patients. We examined whether young adult medical marijuana patients reported health conditions and motivations for use that were consistent with medical use of marijuana in California. Methods: Young adults (N = 366) aged 18 to 26 years were sampled in Los Angeles in 2014–2015 and segmented into medical marijuana ‘patients’ (n = 210), marijuana users with a current recommendation, and non-patient users or ‘non-patients’ (n = 156), marijuana users who never had a medical marijuana recommendation. Differences between patients and non-patients regarding self-reported health histories and past/current motivations for marijuana use were expressed as unadjusted risk ratios. Results: Compared with non-patients, patients were significantly more likely to report a range of lifetime health problems, such as psychological, physical pain and gastrointestinal. In the past 90 days, patients were significantly more likely to report motivations for marijuana use than non-patients concerning sleep, anxiety, physical pain and focusing. Psychological and pain problems were the most common health conditions reported to receive a medical marijuana recommendation. Patients were significantly less likely than non-patients to report any privacy concerns about obtaining a medical marijuana recommendation. Conclusions: Patients were significantly more likely to report a range of health conditions and motivations associated with medical use than non-patients. A great majority of patients reported obtaining a medical marijuana recommendation for health problems in accordance with the California law. [Lankenau SE, Ataiants J,Mohanty S, Schrager S, Iverson E, Wong CF.Health conditions and motivations for marijuana use among young adultmedical marijuana patients and non-patient marijuana users. Drug Alcohol Rev 2017;00:000-000]

Lankenau, S. E., A. Kioumarsi, et al. "Becoming a medical marijuana user." International Journal of Drug Policy **52**: 62-70.

BackgroundSince marijuana became legal for medical use in California in 1996, reasons for medical use among medical marijuana patients (MMP) have become increasingly well described in qualitative studies. However, few studies have detailed how the use of marijuana for medical purposes fits into the broader career trajectories of either becoming a marijuana user or becoming a MMP, including the social influences on medical use.

Lapoint, J., S. Meyer, et al. (2018). "Cannabinoid Hyperemesis Syndrome: Public Health Implications and a Novel Model Treatment Guideline." Western Journal of Emergency Medicine **19**(2): 380-386.

INTRODUCTION: Cannabinoid hyperemesis syndrome (CHS) is an entity associated with cannabinoid overuse. CHS typically presents with cyclical vomiting, diffuse abdominal pain, and relief with hot showers. Patients often present to the emergency department (ED) repeatedly and undergo extensive evaluations including laboratory examination, advanced imaging, and in some cases unnecessary procedures. They are exposed to an array of pharmacologic interventions including opioids that not only lack evidence, but may also be harmful. This paper presents a novel treatment guideline that highlights the identification and diagnosis of CHS and summarizes treatment strategies aimed at resolution of symptoms, avoidance of unnecessary opioids, and ensuring patient safety. METHODS: The San Diego Emergency Medicine Oversight Commission in collaboration with the County of San Diego Health and Human Services Agency and San Diego Kaiser Permanente Division of Medical Toxicology created an expert consensus panel to establish a guideline to unite the ED community in the treatment of CHS. RESULTS: Per the consensus guideline, treatment should focus on symptom relief and education on the need for cannabis cessation. Capsaicin is a readily available topical preparation that is reasonable to use as first-line treatment. Antipsychotics including haloperidol and olanzapine have been reported to provide complete symptom relief in limited case studies. Conventional antiemetics including antihistamines, serotonin antagonists, dopamine antagonists and benzodiazepines may have limited effectiveness. Emergency physicians should avoid opioids if the diagnosis of CHS is certain and educate patients that cannabis cessation is the only intervention that will provide complete symptom relief. CONCLUSION: An expert consensus treatment guideline is provided to assist with diagnosis and appropriate treatment of CHS. Clinicians and public health officials should identity and treat CHS patients with strategies that decrease exposure to opioids, minimize use of healthcare resources, and maximize patient safety.

Larsen, C. and J. Shahinas (2020). "Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials." J Clin Med Res **12**(3): 129-141.

Considering data from in vitro and in vivo studies, cannabidiol (CBD) seems to be a promising candidate for the treatment of both somatic and psychiatric disorders. The aim of this review was to collect dose(s), dosage schemes, efficacy and safety reports of CBD use in adults from clinical studies. A systematic search was performed in PubMed, Embase and Cochrane library for articles published in English between January 1, 2000 and October 25, 2019. The search terms used were related to cannabis and CBD in adults. We identified 25 studies (927 patients; 538 men and 389 women), of which 22 studies were controlled clinical trials (833 patients) and three were observational designs (94 patients) from five countries. Formulations, dose and dosage schemes varied significantly between studies. Varying effects were identified from the randomized controlled trials (RCTs), more apparent effects from non-RCTs and minor safety issues in general. From the controlled trials, we identified anxiolytic effects with acute CBD administration, and therapeutic effects for social anxiety disorder, psychotic disorder and substance use disorders. In general, studies were heterogeneous and showed substantial risks of bias. Although promising results have been identified, considerable variation in dosage schemes and route of administration were employed across studies. There was evidence to support single dose positive effect on social anxiety disorder, short medium-term effects on symptomatic improvement in schizophrenia and lack of effect in the short medium-term on cognitive functioning in psychotic disorders. Overall, the administration was well tolerated with mild side effects.

Lashley, K. and T. G. Pollock (2019). "Waiting to Inhale: Reducing Stigma in the Medical Cannabis Industry." Administrative Science Quarterly **65**(2): 434-482.

When a new industry category is predicated on a product or activity subject to “core” stigma-meaning its very nature is stigmatized-the actors trying to establish it may struggle to gain the resources they need to survive and grow. To explain the process of reducing an industry category’s stigma, we take an inductive approach to understanding how actors in the U.S. medical cannabis industry collectively attempted to create and disseminate a moral public image based on healing and patients? rights. We find that reducing category-level core stigma is a phased effort that takes place across different relational spaces. A moral agenda based on broadly acceptable values jumpstarts the process, and the industry then creates a new moral prototype reflecting these values that industry actors can identify with. Category members must publicly disidentify with the current, stigmatized prototypes and infuse the new moral prototype among their stakeholder audiences through their language and practices, creating emotional connections that lead to cognitive acceptance. This process is messy, as individual organizations often need to continue engaging in stigmatized behaviors to survive, even as they publicly disidentify with them. Our process model also identifies ways in which category emergence in core-stigmatized categories differs from the process for non-stigmatized categories.

Laux, L. C., E. M. Bebin, et al. (2019). "Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results." Epilepsy Res 154: 13-20.

BACKGROUND: Since 2014, patients with severe treatment-resistant epilepsies (TREs) have been receiving add-on cannabidiol (CBD) in an ongoing, expanded access program (EAP), which closely reflects clinical practice. We conducted an interim analysis of long-term efficacy and tolerability in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) who received CBD treatment through December 2016. METHODS: Children and adults with LGS/DS taking stable doses of antiepileptic drugs (AEDs) at baseline were included from 25 EAP sites across the United States. During the 4-week baseline period, parents/caregivers kept diaries of all countable seizure types. Patients received a pharmaceutical formulation of highly purified CBD (Epidiolex(R); 100 mg/mL) in oral solution at 2-10 mg/kg/day, titrated until tolerability limit or a maximum dose of 25-50 mg/kg/day. Patient visits were every 2-4 weeks. The percentage change from baseline in median monthly convulsive (ie, major motor) and total seizures was evaluated at 12-week intervals through 96 weeks. The percentages of patients who had >/=50%, >/=75%, and 100% reduction in monthly seizures relative to the baseline period were also evaluated. Adverse events (AEs) were monitored and summarized for the safety analysis set (SAS) through 144 weeks. RESULTS: Of the 607 patients in the SAS, 58 had DS and 94 had LGS (N = 152); 455 patients had other TREs. Twenty-eight percent of LGS/DS patients withdrew, primarily owing to lack of efficacy (20%). LGS/DS patients were taking a median of 3 (0-10) concomitant AEDs. Median treatment duration was 78.3 (range, 4.1-146.4) weeks. Between weeks 12 and 96, median CBD dose ranged from 21 to 25 mg/kg/day. At 12 weeks, add-on CBD reduced median monthly major motor seizures by 50% and total seizures by 44%, with consistent reductions in both seizure types through 96 weeks. At 12 weeks, the proportions of patients with >/=50%, >/=75%, and 100% reductions in major motor seizures were 53%, 23%, and 6%; the proportions with corresponding reductions in total seizures were 46%, 26%, and 5%. Responder rates for both seizure types were consistent through 96 weeks. CBD had an acceptable safety profile; the most common AEs were somnolence (30%) and diarrhea (24%). CONCLUSIONS: Results from this interim analysis support add-on CBD as an effective long-term treatment option in LGS or DS.

Lee, Y.-H., Y.-C. Chang, et al. (2020). "Is Medical Marijuana Legalization Associated With Prescription Drug Misuse, Illicit Drug Use, or Combination of Both Among Adults in the United States?" Journal of drug issues **50**.

This research focuses on associations of medical marijuana legalization with prescription drug misuse, illicit drug use, and a combination of both behaviors. Using three waves of the National Survey of Drug Use and Health (NSDUH, 2016–2018), adult participants (age ≥ 18) were selected for the final study sample (n = 127,438). Multinomial logistic regression was adjusted for biological, socioeconomic, and substance use measurements. Results from multinomial regression demonstrated that medical marijuana legalization was positively associated with illicit drug use (relative risk ratio [RRR] = 1.33, 95% confidence interval [CI] = [1.17, 1.51]; p < .01) and both prescription drug misuse and illicit drug use (RRR = 1.14, 95% CI = [1.05, 1.25]; p < .01) among U.S. adults. It is recommended to design policy interventions to counter illicit drug use and a combination of both prescription drug misuse and illicit drug use as the result of medical marijuana legalization.

Lee, G., B. Grovey, et al. (2018). "Medical Cannabis for Neuropathic Pain." Current Pain and Headache Reports **22**(1): 8.

Many cultures throughout history have used cannabis to treat a variety of painful ailments. Neuropathic pain is a complicated condition that is challenging to treat with our current medications. Recent scientific discovery has elucidated the intricate role of the endocannabinoid system in the pathophysiology of neuropathic pain. As societal perceptions change, and legislation on medical cannabis relaxes, there is growing interest in the use of medical cannabis for neuropathic pain.

Levine, M., A. Jontz, et al. (2020). "Prevalence of marijuana use among trauma patients before and after legalization of medical marijuana: The Arizona experience." Subst Abus: 1-6.

In recent years, marijuana has become legal for use in many states, for either medicinal or recreational purposes. Objective: The primary objective is to determine if legalization of medical marijuana is associated with an increased use among trauma patients. Methods: Prospective observational study included three periods; (pre-legalization; period 1); legal to grow for medicinal purposes but no dispensaries open (period 2); and legal to purchase medicinal marijuana in a dispensary (period 3). The study included all adult trauma patients presenting to an urban level I trauma center in Phoenix, AZ. The prevalence of use (as defined by positive urine drug screen or self-reporting) in each time period was determined and compared using two sample tests of proportion. Confidence intervals for prevalence (self-reporting only) were compared with published age matched data from the same geographical region of the general population. Results: The prevalence of marijuana use increased significantly from pre-legalization (period 1) to post legalization (periods 2 and 3), but there was no significant change between the two post legalization periods. After controlling for age and sex, the odds of being marijuana positive post-legalization vs. pre-legalization was 1.36, p = 0.006 95%CI [1.09-1.7]. Overall, the prevalence of marijuana among trauma patients was nearly four-fold higher than the population as a whole in the same geographic region. Patients who use marijuana are more likely to use cocaine or amphetamine (OR 2.31; 95% CI 1.86-2.89) or had an ethanol level above 80 mg/dL (OR 1.57; 95% CI 1.32-1.87). Conclusion: The legalization of medicinal marijuana is associated with significantly increased prevalence among trauma patients. It appears that legalization, rather than the convenience of dispensaries, is associated with an increase in use.

Levinsohn, E. A. and K. P. Hill (2020). "Clinical uses of cannabis and cannabinoids in the United States." Journal of the Neurological Sciences **411**: 116717.

The role of cannabis in medicine is rapidly evolving. Medical cannabis is now legal in a majority of states, and THC and CBD, the prominent cannabinoids found in cannabis, have both been utilized in the development of FDA-approved drugs. Due to the complicated legal status of cannabis and cannabinoids, as well as regulations that vary from state to state, the appropriate use of these substances for both patients as well as clinicians is often unclear. Advancements in the understanding of the pharmacology of cannabis have led to numerous proposed uses of these drugs, including as antidepressant or analgesic agents. However, clinical trial data for these substances suggests that many purported indications of cannabis and cannabinoids are not supported by good clinical data. Furthermore, cannabis and several cannabinoid-based medications have potentially concerning side effect profiles that may limit their use in certain patient populations. As the legal status and clinical database of these medications continue to evolve, physicians will need to continue to balance the real potential of these compounds with their limitations and adverse effects.

Li, Y. and M. A. Palma (2018). "Investigating the effects of medical marijuana laws on educational attainment." Economics Letters **164**: 43-45.

From 1996 to 2013, a total of 19 states and Washington, D.C. adopted medical marijuana laws (MML). Early adolescent marijuana use correlates with several problems later in life, including job-related skill acquisition, illegal substance abuse, and educational attainment. This paper examines the negative externalities of MML on educational attainment by applying a difference-in-differences research design. The results show that MML decrease high school graduation rates by 0.36 percentage points, indicating that nearly 13,000 students will not graduate as a result of the MML implementation.

Likar, R., M. Köstenberger, et al. (2017). "Clinical use of cannabinoids." PHARMAKON **5**(2): 137-141.

Cannabinoids are an interesting possibility for pain therapy as add-on therapy, if no sufficient pain relief can be achieved with other analgesics. The use of cannabinoids is only indicated for chronic pain and not for acute pain. An important basic principle of therapy is ,,start low and go slow", as side effects can be reduced or avoided altogether. The most important counter indication is the personal or family medical history regarding psychosis, schizophrenia and unstable ischemic cardiac illness. There are some concerns about use with pregnant and lactating patients and those with severe liver and kidney disease. With older patients the lowest dosage of cannabinoids should be initially used. Similar to opioids, the risks of misuse should always be taken into consideration.

Likar, R. and G. Nahler (2017). "The use of cannabis in supportive care and treatment of brain tumor." Neuro-Oncology Practice **4**(3): 151-160.

Cannabinoids are multitarget substances. Currently available are dronabinol (synthetic delta-9-tetrahydrocannabinol, THC), synthetic cannabidiol (CBD) the respective substances isolated and purified from cannabis, a refined extract, nabiximols (THC:CBD = 1.08:1.00); and nabilone, which is also synthetic and has properties that are very similar to those of THC. Cannabinoids have a role in the treatment of cancer as palliative interventions against nausea, vomiting, pain, anxiety, and sleep disturbances. THC and nabilone are also used for anorexia and weight loss, whereas CBD has no orexigenic effect. The psychotropic effects of THC and nabilone, although often undesirable, can improve mood when administered in low doses. CBD has no psychotropic effects; it is anxiolytic and antidepressive. Of particular interest are glioma studies in animals where relatively high doses of CBD and THC demonstrated significant regression of tumor volumes (approximately 50% to 95% and even complete eradication in rare cases). Concomitant treatment with X-rays or temozolomide enhanced activity further. Similarly, a combination of THC with CBD showed synergistic effects. Although many questions, such as on optimized treatment schedules, are still unresolved, today’s scientific results suggest that cannabinoids could play an important role in palliative care of brain tumor patients.

Linares, I. M. P., J. A. S. Crippa, et al. (2017). Chapter 91 - Beneficial Effects of Cannabis and Related Compounds on Sleep A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 877-882.

Abstract The plant Cannabis sativa, known as marijuana, is composed of more than 60 cannabinoids, which may have different effects on the sleep-wake cycle. The two main components of the plant are Δ9-tetrahydrocannabinol (THC), which is responsible for psychoactive effects, and cannabidiol (CBD), the main component of the plant that does not have psychological or behavioral effects. Other substances found in marijuana are: (1) cannabinol, which has a slightly less powerful effect than THC; (2) cannabigerol, a substance that is not as psychoactive as CBD; and (3) β-caryophyllene. The aim of this chapter is to describe the effects of cannabis and its components on the sleep-wake cycle.

Lintzeris, N., A. Bhardwaj, et al. (2019). "Nabiximols for the Treatment of Cannabis Dependence: A Randomized Clinical Trial." JAMA Intern Med.

Importance: There are no effective medications for treating dependence on cannabis. Objective: To examine the safety and efficacy of nabiximols in the treatment of patients with cannabis dependence. Design, Setting, and Participants: This parallel double-blind randomized clinical trial comparing nabiximols with placebo in a 12-week, multisite outpatient study recruited participants from February 3, 2016, to June 14, 2017, at 4 outpatient specialist alcohol and drug treatment services in New South Wales, Australia. Participants had cannabis dependence (as defined by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) and were seeking treatment, were nonresponsive to prior treatment attempts, were 18 to 64 years of age, had no other substance use disorder, had no severe medical or psychiatric conditions, were not pregnant, were not mandated by a court to undergo treatment, and provided informed consent. Results for primary efficacy measures and all secondary outcomes were obtained using a modified intention-to-treat data set. Interventions: Participants received 12-week treatment involving weekly clinical reviews, structured counseling, and flexible medication doses-up to 32 sprays daily (tetrahydrocannabinol, 86.4 mg, and cannabidiol, 80 mg), dispensed weekly. Main Outcomes and Measures: Primary outcome was self-reported number of days using illicit cannabis during the 12-week period. Other outcomes included alternate cannabis use parameters (periods of abstinence, withdrawal, cravings, and problems), safety parameters (adverse events and aberrant medication use), health status, other substance use, and treatment retention. Results: A total of 128 participants (30 women and 98 men; mean [SD] age, 35.0 [10.9] years) were randomized and received at least 1 dose of study medication. Participants had used a mean (SD) of 2.3 (2.1) g of cannabis on a mean (SD) of 25.7 (4.5) days in the past 28 days. Treatment retention was comparable for the 2 groups (placebo, 30 of 67 participants [44.8%]; nabiximols, 30 of 61 participants [49.2%]), and both groups used similar mean (SD) doses (placebo, 18.5 [9.5] sprays daily; nabiximols, 17.6 [9.5] sprays daily, equivalent to a mean [SD] of 47.5 [25.7] mg of tetrahydrocannabinol and 44.0 [23.8] mg of cannabidiol). For the primary end point, the placebo group reported significantly more days using cannabis during the 12 weeks (mean [SD], 53.1 [33.0] days) than the nabiximols group (mean [SD], 35.0 [32.4] days; estimated difference, 18.6 days; 95% CI, 3.5-33.7 days; P = .02). Both groups showed comparable improvements in health status, with no substantial changes in other substance use. Medication was well tolerated with few adverse events. Conclusions and Relevance: This study demonstrates that cannabinoid agonist treatment, in this case using nabiximols, in combination with psychosocial interventions is a safe approach for reducing cannabis use among individuals with cannabis dependence who are seeking treatment. Trial Registration: anzctr.org.au Identifier: ACTRN12616000103460.

Lintzeris, N., Driels, J., Elias, N., Arnold, J., McGregor, I., Allsop, D. (2018). "Medicinal cannabis in Australia, 2016: the Cannabis as Medicine Survey (CAMS-16)." Medical Journal of Australia, **209**(5): 211-216.

Objective: To explore patterns of cannabis use for medical purposes in Australia immediately prior to the 2016 legislation for frameworks for medical cannabis use.  
Design, setting: Anonymous online survey with convenience sample, April–October 2016. Participants were recruited through online media and at professional and consumer forums.\  
Participants: Adults (at least 18 years of age) who reported using a cannabis product for self-identified medical or therapeutic reasons during the preceding 12 months.  
Main outcome measures: Consumer characteristics; indications and patterns of medical cannabis use; perceived benefits and harms; views on appropriate availability of medical cannabis.  
Results: Most of the 1748 participants were men (68.1%) and employed (56.6%), with a mean age of 37.9 years (SD, 13.4 years) and mean reported period of medical cannabis use of 9.8 years (SD, 12.5 years). The most frequent reasons for medical cannabis use were anxiety (50.7%), back pain (50.0%), depression (49.3%), and sleep problems (43.5%). Respondents had used medical cannabis on a mean of 19.9 of the previous 28 days (SD, 10.0 days), spending a mean $68.60 (SD, $85.00) per week, and 83.4% had inhaled the substance. Participants reported high levels of clinical effectiveness and frequent side effects, including drowsiness, ocular irritation, lethargy and memory impairment; 17% met DSM-5 criteria for moderate or severe cannabis use disorder. Many reported harms or concerns related to the illicit status of cannabis. Participants believed that medical cannabis should be integrated into mainstream health care, and that products should be required to meet consistency and safety standards.  
Conclusion: Illicitly sourced cannabis is used to treat a broad range of medical conditions in Australia. Future models of prescribed medical cannabis take consumer patterns of use and demand into consideration.

Lintzeris, N., L. Mills, et al. (2020). Medical cannabis use in the Australian community following introduction of legal access: The 2018-2019 Online Cross-Sectional Cannabis as Medicine Survey (CAMS-18).

Background : In 2016 the Australian federal government passed legislation enabling a range of cannabis-based products to be prescribed to patients by registered healthcare professionals. An online survey conducted immediately prior to these legislative changes found that the vast majority of respondents at the time were illicitly sourcing cannabis plant matter, smoking was the preferred route of administration, and mental health, chronic pain, and sleep conditions were the most frequently cited reasons for medical cannabis use. This manuscript reports the results of a follow-up survey conducted in 2018-2019, the Cannabis As Medicine Survey (CAMS-18). The goal of this second questionnaire was to examine patterns of use and consumer perspectives regarding medical cannabis use in Australia, two years after the introduction of legal access pathways. Methods : Anonymous online cross-sectional survey with convenience sample, recruited mainly through online media between September 2018 and March 2019. Participants were adults (18 years or over) residing in Australia who reported using a cannabis product for self-identified therapeutic reasons during the preceding 12 months. The survey measured consumer characteristics; indications and patterns of medical cannabis use; routes and frequency of administration; perceived benefits and harms; experiences and preferred models of access to medical cannabis. Results : Data were available for 1388 respondents. The main categories of condition being treated with medical cannabis were pain (36.4%), mental health (32.8%), sleep (9.2%), neurological (5.2%) and cancer (3.8%). Respondents reported using medical cannabis on 15.8 (11.2) days in the past 28, by inhaled (71.4%) or oral (26.5%) routes and spending AUD$82.27 ($101.27) per week. There were high levels of self-reported effectiveness, but also high rates of side effects. There was uncertainty regarding the composition of illicit cannabinoid products and concerns regarding their possible contamination. Few respondents (2.7%) had accessed legally prescribed medical cannabis, with the main perceived barriers being cost, dis-interest from the medical profession, and stigma regarding cannabis use. Conclusions : Chronic pain, mental health and sleep remain the main clinical conditions for which consumers report using medical cannabis. Despite two years of legal availability, most consumers in Australia reported accessing illicit cannabis products, with uncertainty regarding the quality or composition of cannabis products.

Lintzeris, N., L. Mills, et al. (2020). "Cannabis use in patients 3 months after ceasing nabiximols for the treatment of cannabis dependence: Results from a placebo-controlled randomised trial." Drug and Alcohol Dependence **215**: 108220.

Introduction and Aims Previous studies suggest cannabinoid agonist treatment is effective in reducing cannabis use in dependent treatment seekers, however few studies have reported on post-treatment outcomes. We examine cannabis use outcomes 12 weeks after cessation of treatment from a randomised placebo-controlled trial of nabiximols for the treatment of cannabis dependence. Method 128 participants received either nabiximols (n = 61) or placebo (n = 67) for 12 weeks, in combination with psychosocial interventions. Self-reported number of days of cannabis use in the previous 28 days was measured at baseline, 4, 8, and 12 weeks (end of treatment) and again at 24 weeks (3 months after treatment ceased). Urinalysis was used to confirm self-report data at Week 24 interview. Results A factorial mixed-effects model for repeated measures regression revealed that the nabiximols group used cannabis on 6.8 fewer days in the previous 28 days at week 12 (end of treatment) than the placebo group (p = 0.002, CI: 2.1,11.4), and 6.7 fewer days in the previous 28 days at the week-24 follow-up than the placebo group (p = 0.006, CI: 1.4,12.1). A significantly higher proportion of the nabiximols group (14/61; 23 %) than the placebo group (6/67; 9%) reported abstinence from cannabis in the previous 28 days at the week-24 research interview OR=3.0, CI: 1.1, 9.1; p=0.035, NNT=8, CI: 4, 71). Discussions and Conclusions The benefits of treatment incorporating nabiximols with psychosocial interventions in reducing cannabis use appears to persist for up to 3 months after the cessation of treatment. A stepped care model of treatment is proposed. Trial Registration Australian New Zealand Clinical Trials Registry (ACTRN12616000103460) https://www.anzctr.org.au

Lopez, C. D., V. Boddapati, et al. (2020). "State Medical Cannabis Laws Associated With Reduction in Opioid Prescriptions by Orthopaedic Surgeons in Medicare Part D Cohort." J Am Acad Orthop Surg.

INTRODUCTION: Opioid prescriptions and abuse remain a significant national concern. Cannabinoids offer a potentially attractive nonopioid analgesic option for orthopaedic patients, and 32 US states have passed medical cannabis laws (MCLs), legalizing patient access to cannabinoids. We examine the association between implementation of state cannabis laws and prescribing patterns for opioids by orthopaedic surgeons in Medicare Part D patients between 2013 and 2017. METHODS: Using the Medicare Part D Prescription Drug Event database, we measured annual aggregate daily doses of all opioid medications (excluding buprenorphine) prescribed by orthopaedic surgeons in each US state (and DC), in addition to total daily doses of opioid medications by generic name (hydrocodone, oxycodone, fentanyl, morphine, methadone, and "other opioids"). We used adjusted linear regression models to examine associations between state-specific cannabis regulations (state MCL, MCL type-dispensary or home cultivation, and recreational cannabis legalization) and annual total daily doses of opioid medications (all opioids and opioid types, separately). RESULTS: State MCLs were associated with a statistically significant reduction in aggregate opioid prescribing of 144,000 daily doses (19.7% reduction) annually (95% confidence interval [CI], -0.535 to -0.024 million; P < 0.01). States with MCLs allowing access to in-state dispensaries had a statistically significant reduction in total opioid prescriptions of 96,000 daily doses (13.1%) annually (95% CI, -0.165 to -0.026 million; P < 0.01). Specifically, MCLs were associated with a statistically significant reduction of 72,000 daily doses of hydrocodone annually (95% CI, -0.164 to -0.019 million; P < 0.01). No significant association between recreational marijuana legalization and opioid prescribing was found. CONCLUSION: Orthopaedic surgeons are among the highest prescribers of opioids, highlighting the importance of providing nonopioid analgesic alternatives in efforts to reduce opioid use in the patient cohort. This study is the first to examine the association between implementation of state cannabis laws and prescribing patterns for opioids by orthopaedic surgeons in Medicare Part D patients. LEVEL OF EVIDENCE: Population-based ecological study.

Lovell, M. E., R. Bruno, et al. (2018). "Cognitive, physical, and mental health outcomes between long-term cannabis and tobacco users." Addictive Behaviors **79**: 178-188.

Introduction Cannabis intoxication adversely affects health, yet persistent effects following short-term abstinence in long-term cannabis users are unclear. This matched-subjects, cross-sectional study compared health outcomes of long-term cannabis and long-term tobacco-only users, relative to population norms. Methods Nineteen long-term (mean 32.3years of use, mean age 55.7years), abstinent (mean 15h) cannabis users and 16 long-term tobacco users (mean 37.1years of use, mean age 52.9years), matched for age, educational attainment, and lifetime tobacco consumption, were compared on measures of learning and memory, response inhibition, information-processing, sustained attention, executive control, and mental and physical health. Results Cannabis users exhibited poorer overall learning and delayed recall and greater interference and forgetting than tobacco users, and exhibited poorer recall than norms. Inhibition and executive control were similar between groups, but cannabis users had slower reaction times during information processing and sustained attention tasks. Cannabis users had superior health satisfaction and psychological, somatic, and general health than tobacco users and had similar mental and physical health to norms whilst tobacco users had greater stress, role limitations from emotional problems, and poorer health satisfaction. Conclusions Long-term cannabis users may exhibit deficits in some cognitive domains despite short-term abstinence and may therefore benefit from interventions to improve cognitive performance. Tobacco alone may contribute to adverse mental and physical health outcomes, which requires appropriate control in future studies.

Lucas, P., E. P. Baron, et al. (2019). "Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients." Harm Reduct J **16**(1): 9.

BACKGROUND: A 239-question cross-sectional survey was sent out via email in January 2017 to gather comprehensive information on cannabis use from Canadian medical cannabis patients registered with a federally authorized licensed cannabis producer, resulting in 2032 complete surveys. METHODS: The survey gathered detailed demographic data and comprehensive information on patient patterns of medical cannabis use, including questions assessing the self-reported impact of cannabis on the use of prescription drugs, illicit substances, alcohol, and tobacco. RESULTS: Participants were 62.6% male (n = 1271) and 91% Caucasian (n = 1839). The mean age was 40 years old, and pain and mental health conditions accounted for 83.7% of all respondents (n = 1700). Then, 74.6% of respondents reported daily cannabis use (n = 1515) and mean amount used per day was 1.5 g. The most commonly cited substitution was for prescription drugs (69.1%, n = 953), followed by alcohol (44.5%, n = 515), tobacco (31.1%, n = 406), and illicit substances (26.6%, n = 136). Opioid medications accounted for 35.3% of all prescription drug substitution (n = 610), followed by antidepressants (21.5%, n = 371). Of the 610 mentions of specific opioid medications, patients report total cessation of use of 59.3% (n = 362). CONCLUSIONS: This study offers a unique perspective by focusing on the use of a standardized, government-regulated source of medical cannabis by patients registered in Canada's federal medical cannabis program. The findings provide a granular view of patient patterns of medical cannabis use, and the subsequent self-reported impacts on the use of opioids, alcohol, and other substances, adding to a growing body of academic research suggesting that increased regulated access to medical and recreational cannabis can result in a reduction in the use of and subsequent harms associated with opioids, alcohol, tobacco, and other substances.

Lucas, C. J., P. Galettis, et al. (2018). "Cannabinoid Disposition After Human Intraperitoneal Use: AnInsight Into Intraperitoneal Pharmacokinetic Properties in Metastatic Cancer." Clin Ther **40**(9): 1442-1447.

BACKGROUND: Medicinal cannabis is prescribed under the provision of a controlled drug in the Australian Poisons Standard. However, multiple laws must be navigated in order for patients to obtain access and imported products can be expensive. Dose-response information for both efficacy and toxicity pertaining to medicinal cannabis is lacking. The pharmacokinetic properties of cannabis administered by traditional routes has been described but to date, there is no literature on the pharmacokinetic properties of an intraperitoneal cannabinoid emulsion. CASE DESCRIPTION: A cachectic 56-year-old female with stage IV ovarian cancer and peritoneal metastases presented to hospital with fevers, abdominal distension and severe pain, vomiting, anorexia, dehydration and confusion. The patient reported receiving an intraperitoneal injection, purported to contain 12g of mixed cannabinoid (administered by a deregistered medical practitioner) two days prior to presentation. Additionally, cannabis oil oral capsules were administered in the hours prior to hospital admission. RESULTS: THC concentrations were consistent with the clinical state but not with the known pharmacokinetic properties of cannabis nor of intraperitoneal absorption. THC concentrations at the time of presentation were predicted to be ~60ng/mL. Evidence suggests that blood THC concentrations >5ng/mL are associated with substantial cognitive and psychomotor impairment. The predicted time for concentrations to drop <5ng/mL was 49days after administration. DISCUSSION: The unusual pharmacokinetic properties of the case suggest that there is a large amount unknown about cannabis pharmacokinetic properties. The pharmacokinetic properties of a large amount of a lipid soluble compound given intraperitoneally gave insights into the absorption and distribution of cannabinoids, particularly in the setting of metastatic malignancy.

Lucas, P. and Z. Walsh (2017). "Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients." International Journal of Drug Policy **42**: 30-35.

Background: In 2014 Health Canada replaced the Marihuana for Medical Access Regulations (MMAR) with the Marihuana for Medical Purposes Regulations (MMPR). One of the primary changes in the new program has been to move from a single Licensed Producer (LP) of cannabis to multiple Licensed Producers. This is the first comprehensive survey of patients enrolled in the MMPR.

Macari, D. M., B. Gbadamosi, et al. (2020). "Medical Cannabis in Cancer Patients: A Survey of a Community Hematology Oncology Population." Am J Clin Oncol.

OBJECTIVES: Cancer patients are using medical cannabis (MC) to address symptoms; however, little data exist to guide clinicians when counseling patients. We seek to define the patterns of MC use among cancer patients, as well as efficacy and safety of MC. MATERIALS AND METHODS: Cancer patients attending oncology office visits at Beaumont Hospital, Michigan from July to December 2018 were anonymously surveyed. The survey included data regarding demographics, diagnosis, treatment, symptom burden, and MC use. Patients who reported MC use since their cancer diagnosis completed a section on patterns of use, efficacy, and safety. RESULTS: The response rate was 188 of 327 (57.5%). MC use was reported by 46 of 188 (24.5%). A median composite baseline symptom score ranging from 8 (best) to 32 (worst) was higher in patients using MC versus nonusers; 17.5 versus 14.4 (P<0.001). Pain was the symptom with the highest frequency of improvement 34/42 (81%), followed by appetite 34/44 (77.3%), and anxiety 32/44 (73%). MC improved the ability to tolerate treatment in 24/44 (54.5%). Cloudy thinking is the symptom that worsened the most 7/42 (16.7%), with decreased energy being experienced by 4/41 (9.8%) of the users. CONCLUSIONS: MC was utilized by a significant portion of cancer patients in this sample, across age, diagnosis, stage, and treatment. Patients with a higher severity of baseline symptoms were more likely to use MC and report a favorable efficacy profile of MC. Minimal toxicity was reported in this cohort. Prospective studies are needed to define the efficacy and safety of MC.

MacCallum, C. A. and E. B. Russo (2018). "Practical considerations in medical cannabis administration and dosing." European Journal of Internal Medicine **49**: 12-19.

Cannabis has been employed medicinally throughout history, but its recent legal prohibition, biochemical complexity and variability, quality control issues, previous dearth of appropriately powered randomised controlled trials, and lack of pertinent education have conspired to leave clinicians in the dark as to how to advise patients pursuing such treatment. With the advent of pharmaceutical cannabis-based medicines (Sativex/nabiximols and Epidiolex), and liberalisation of access in certain nations, this ignorance of cannabis pharmacology and therapeutics has become untenable. In this article, the authors endeavour to present concise data on cannabis pharmacology related to tetrahydrocannabinol (THC), cannabidiol (CBD) et al., methods of administration (smoking, vaporisation, oral), and dosing recommendations. Adverse events of cannabis medicine pertain primarily to THC, whose total daily dose-equivalent should generally be limited to 30mg/day or less, preferably in conjunction with CBD, to avoid psychoactive sequelae and development of tolerance. CBD, in contrast to THC, is less potent, and may require much higher doses for its adjunctive benefits on pain, inflammation, and attenuation of THC-associated anxiety and tachycardia. Dose initiation should commence at modest levels, and titration of any cannabis preparation should be undertaken slowly over a period of as much as two weeks. Suggestions are offered on cannabis-drug interactions, patient monitoring, and standards of care, while special cases for cannabis therapeutics are addressed: epilepsy, cancer palliation and primary treatment, chronic pain, use in the elderly, Parkinson disease, paediatrics, with concomitant opioids, and in relation to driving and hazardous activities.

MacMillan, K., A. Keddy, et al. (2019). "Cannabis and glaucoma: A literature review." DALHOUSIE MEDICAL JOURNAL **46**.

Introduction: Primary open-angle glaucoma (POAG) is characterized by the loss of retinal ganglion cells secondary to optic neuropathy; increased intraocular pressure (IOP) may or may not be present. Many treatment options focus on decreasing IOP measurements to attempt to prevent progression of glaucoma. Our literature review addressed a relatively common question; if cannabis is effective for treating elevated IOP in patients with glaucoma. Objective: To evaluate the current evidence for the use of cannabis for reducing IOP in glaucoma. Methods: PubMed, Embase, and the Cochrane Database were searched along with references drawn from full text articles published before January 2018 for the best available evidence that met the inclusion criteria.Three authors independently evaluated and selected the articles that represented the best available evidence.The selected articles were chosen based on study methodology and the type of cannabis used for the treatment of glaucoma. Randomized Control Trials were preferred, although lacking. No studies directly compared cannabis to the current standard of care medications for lowering IOP. Results: Five randomized controlled trials were included as best available evidence although they used different routes of administration. All studies included compared cannabis to placebo. The studies evaluated showed a range of IOP lowering effects and side effects.Topical administration has shown conflicting results for the treatment of glaucoma.Conclusion:The many forms of cannabinoid administration have demonstrated variable levels of effectiveness. The variability of the studies indicates the need for more research. Specifically, larger sample sizes, and comparison of standardized cannabis to current standards of care instead of placebo are strongly encouraged.

Madden, K., A. George, et al. (2019). "Cannabis for pain in orthopedics: a systematic review focusing on study methodology." Canadian journal of surgery. Journal Canadien de chirurgie 62: 001018.

Background: Medical cannabis use is an emerging topic of interest in orthopedics. Although there is a large amount of literature on medical cannabis use for managing various types of pain, few studies have focused on orthopedic conditions. There is little high-quality evidence in core orthopedic areas. The objective of this study was to summarize the literature on the efficacy of cannabis use for pain related to orthopedic conditions. Methods: We conducted a systematic review of the literature on the use of cannabinoids for pain management in core orthopedic conditions. Two independent reviewers extracted information on reporting quality, risk of bias, drugs, population, control, duration of study, pain outcomes and the authors’ conclusions regarding efficacy for pain outcomes. Results: We identified 33 orthopedic studies, including 21 primary studies and 12 reviews. Study quality was generally low to moderate. Six of the included studies had a control group and 15 were noncontrolled studies. Methodologies, drugs and protocols of administration varied greatly across studies. Study conclusions were generally positive in noncontrolled studies and mixed in controlled studies. Studies using higher doses tended to conclude that cannabis use was effective, but the potential for harmful effects may also be increased with higher doses. Conclusion: Variability in the methodologies used in cannabis research makes it challenging to draw conclusions about dosing, routes and frequency of administration. Most of the existing evidence suggests that medical cannabis use is effective, but this efficacy has been demonstrated only when either there is no comparator or cannabis is compared with placebo. Studies using an active comparator have not demonstrated efficacy. Future research should focus on improving study reporting and methodologic quality so that protocols that optimize pain control while minimizing harmful effects can be determined.

Madden, K., K. Tanco, et al. (2020). "Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol." Pediatrics **145**(6).

The use of cannabidiol products in pediatric patients is becoming more frequent because of the increased ease of accessibility. This case report illustrates the potential for cannabidiol to interact with stable medication regimens. A 13-year-old girl with metastatic cancer and chronic pain presented with increased sleepiness and fatigue. She had been started on 7.5 mg of methadone by mouth twice daily 4 months earlier. Unbeknownst to her physicians, her parents had commenced her on cannabidiol and subsequently increased the dose leading up to her presentation, thinking it would result in tumor shrinkage. The initial serum methadone level was 271 ng/mL, which decreased to 125 ng/mL 14 days after discontinuing cannabidiol. The reduced serum methadone level coincided with improved sleepiness and fatigue. Cannabidiol inhibits CYP3A4 and CYP2C19, both of which are involved in the metabolism of methadone. Pediatricians should be aware of this potential interaction and inquire if their patients are receiving cannabidiol.

Madden, K., N. van der Hoek, et al. (2018). "Cannabinoids in the Management of Musculoskeletal Pain: A Critical Review of the Evidence." JBJS Reviews 6(5).

The purposes of the present scoping review were to identify (1) the available studies regarding the efficacy of cannabinoids for the management of musculoskeletal pain and related conditions and (2) the knowledge gaps and opportunities in this area of research.\*There is little high-quality evidence for medical cannabis in the core orthopaedic areas of arthritis, postoperative pain, back pain, and trauma-related pain.\*The “best available” evidence suggests cannabis can be effective for managing arthritis pain, back pain, Research update –September 2018 and trauma-related pain, although the quality of the evidence is poor.\*Evidence regarding the use of cannabinoids for the management of postoperative pain is mixed.\*Research on pain control in patients with arthritis, conditions related to the spine, and traumatic injuries represents major under-represented areas of study for the role of cannabinoids, and highquality Level-I studies are needed.

Maggio, N., E. Shavit Stein, et al. (2018). "Cannabidiol Regulates Long Term Potentiation Following Status Epilepticus: Mediation by Calcium Stores and Serotonin." Frontiers in Molecular Neuroscience **11**(32).

Epilepsy is a devastating disease, with cognitive and emotional consequences that are not curable. In recent years, it became apparent that cannabinoids help patients to cope with epilepsy. We have studied the effects of cannabidiol (CBD) on the ability to produce long term potentiation (LTP) in stratum radiatum of CA1 region of the mouse hippocampus. Exposure to seizure-producing pilocarpine reduced the ability to generate LTP in the slice. Pre-exposure to CBD prevented this effect of pilocarpine. Furthermore, CBD caused a marked increase in ability to generate LTP, an effect that was blocked by calcium store antagonists as well as by a reduction in serotonin tone. Serotonin, possibly acting at a 5HT1A receptor, or fenfluramine, which causes release of serotonin from its native terminals, mimicked the effect of CBD. It is proposed that CBD enhances non-NMDA LTP in the slice by facilitating release of serotonin from terminals, consequently ameliorating the detrimental effects of pilocarpine.

Maharajan, M. K., Y. J. Yong, et al. (2020). "Medical cannabis for chronic pain: can it make a difference in pain management?" J Anesth **34**(1): 95-103.

Globally, chronic pain is a major therapeutic challenge and affects more than 15% of the population. As patients with painful terminal diseases may face unbearable pain, there is a need for more potent analgesics. Although opioid-based therapeutic agents received attention to manage severe pain, their adverse drug effects and mortality rate associated with opioids overdose are the major concerns. Evidences from clinical trials showed therapeutic benefits of cannabis, especially delta-9-tetrahydrocannabinol and cannabinoids reduced neuropathic pain intensity in various conditions. Also, there are reports on using combination cannabinoid therapies for chronic pain management. The association of cannabis dependence and addiction has been discussed much and the reports mentioned that it can be comparatively lower than other substances such as nicotine and alcohol. More countries have decided to legalise the medicinal use of cannabis and marijuana. Healthcare professionals should keep themselves updated with the changing state of medical cannabis and its applications. The pharmacokinetics and safety of medical cannabis need to be studied by conducting clinical research. The complex and variable chemically active contents of herbal cannabis and methodological limitations in the administration of cannabis to study participants, make the clinical research difficult.

Manzanares, J. and M. S. García-Gutiérrez (2017). "Is the Cannabidiol Potentially Useful for the Treatment of Neuropsychiatric and Drug-Use Disorders?" Res Rev Biosci **12**(1): 112.

Preclinical and clinical evidence collected over the past years suggests that Cannabidiol (CBD), one of the main compounds of the plant Cannabis sativa, presents potential therapeutic activity for the treatment of neuropsychiatric and drug-use disorders. Studies carried out in animal models revealed that CBD presents anxiolytic-like effects in different paradigms such as the Vogel conflict test [1], the elevated plus maze test [2] and the fear conditioning test [3-6]. Antidepressant-like effects were reported in mice following acute or repeated CBD administration in the forced swim [7] and in the tail suspension tests [8]. In addition, CBD decreased defensive behaviors evoked by predator exposure, a proposed model of panic attacks and posttraumatic stress disorder (PTSD) [9,10]. Interestingly, CBD reversed the alteration of prepulse inhibition (PPI) observed in spontaneously hypertensive rats [11] and in a glutamate-based models of psychosis [12] and exhibited a similar profile compared with atypical antipsychotic drugs [13,14]. Indeed, CBD improved cognition in several preclinical models of cognitive impairment [15]. Recent evidences pointed out that CBD might be a potential treatment for drug-use disorders. CBD reduced heroin craving and relapse [16], and cocaine [17] and alcohol consumption mice [18]. In clinical studies, CBD reduced anxiety and the psychotic-like symptoms induced by Δ9-tetrahydrocannabinol (ïÂÂÂÂÂÂ9-THC) [19]. Indeed, CBD reduced anxiety in healthy volunteers [20-22], in treatment-naïve social phobic patients [23] and in posttraumatic stress disorder [24]. Also, CBD reduced the psychotic symptoms in schizophrenia [25,26] and in Parkinson´s disease [27,28].

Maple, K. E., N. E. Wright, et al. (2017). Chapter e7 - Cannabis Use and Attention-Deficit/Hyperactivity Disorder: Potential Moderators A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** e64-e71.

Abstract As discussed in previous chapters, psychiatric disorders are often comorbid with cannabis use. To supplement other chapters covering mood and psychotic disorders, this chapter focuses on the relationship between cannabis use and attention-deficit/hyperactivity disorder (ADHD), and overviews potential moderators of this comorbid relationship. Attention deficits have been observed in cannabis users; ADHD places one at increased risk for early initiation of cannabis use, becoming a heavy user, and developing a cannabis use disorder (CUD). However, the direction of causality in this relationship remains unclear. In addition, factors such as comorbid oppositional defiant disorder (ODD) and conduct disorder (CD) may influence the relationship between cannabis use and ADHD. Lastly, we will discuss the potential influence of THC and CBD content in cannabis samples on the development of psychiatric problems. Overall, more neuroimaging studies and longitudinal research are needed in order to draw sound conclusions in these relatively new areas of research.

Martins-Welch, D., C. Nouryan, et al. (2017). "Health providers’ perspectives on medical marijuana use." Journal of Clinical Oncology **35**(31\_suppl): 235-235.

Background: According to the CDC, 117 million Americans have one or more chronic health conditions and 31% have used two or more prescription drugs in the past month. Approximately 40% of adults in the United States are using some form of Complementary and Alternative Medicine. Medical marijuana is one such medicine, and to date 29 states have legalized medical marijuana. Methods: A multicenter, anonymous, on-line survey of health care providers was distributed via e-mail within a large health system in the NY Metropolitan area. The survey was distributed in April and May of 2017. The specific aim was to collect information about health care providers’ perspectives on the use of MM in general and for specific medical conditions. Results: The sample (n = 137) consisted of 4% RNs, 10% NPs, 10% fellows, 21% resident physicians, and 52% attending physicians. Average experience was 13 years (range: 0-43), half (53%) were under 40 years old and just over half (56%) were female. Most practitioners recognized a benefit of MM for the treatment of cancer-associated symptoms, few were concerned with side effects and 5% of responders answered that MM was not appropriate at any stage of illness. Responders were “most likely to recommend or refer MM if other therapies were not effective” for cancer (83%), chronic pain (68%), spinal cord injury with spasticity (50%), MS (46%), epilepsy (42%), neuropathy (42%) and Parkinson’s disease (41%). Most providers (77%) believed that MM has the potential to reduce overall opioid use, this was found to be statistically more common in younger providers. The most common conditions that providers reported their patients were requesting MM for were cancer (37%), chronic pain (26%) and neuropathy (10%). The most common concerns about MM use were side effects (16%), addiction (13%), legal consequences (11%), cost (7%) and that other providers would judge MM use (7%). Conclusions: Our survey shows that providers are overwhelmingly in support of MM use in patients with chronic illness, particularly in cancer patients. However providers describe significant and practical concerns about MM utilization. Given the rate at which MM is being legalized throughout the country, it is imperative that there be increased focus on education and clinical studies on MM.

Maurya, N. and B. K. Velmurugan (2018). "Therapeutic applications of cannabinoids." Chem Biol Interact **293**: 77-88.

The psychoactive property of cannabinoids is well known and there has been a continuous controversy regarding the usage of these compounds for therapeutic purposes all over the world. Their use for medical and research purposes are restricted in various countries. However, their utility as medications should not be overshadowed by its negative physiological activities. This review article is focused on the therapeutic potential and applications of phytocannabinoids and endocannabinoids. We further highlights their mode of action, overall effects on physiology, various in vitro and in vivo studies that have been done so far and the extent to which these compounds can be useful in different disease conditions such as cancer, Alzheimer's disease, multiple sclerosis, pain, inflammation, glaucoma and many others. Thus, this work is an attempt to make the readers understand the positive implications of these compounds and indicates the significant developments of utilizing cannabinoids as therapeutic agents.

McLennan, A., M. Kerba, et al. (2020). "Health care provider preferences for, and barriers to, cannabis use in cancer care." Current oncology (Toronto, Ont.) **27**(2): e199-e205.

BACKGROUND: Limited research has been conducted about the perspectives of oncology health care providers (hcps) concerning the use of cannabis in cancer care and their potential role in advising patients. We sought to determine the barriers encountered by hcps with respect to medical cannabis and their preferred practices in this area. METHODS: An anonymous survey about cannabis was distributed to oncology hcps at the Tom Baker Cancer Centre in Calgary, Alberta. The 45-question survey measured the opinions of hcps about cannabis use and authorization in oncology. RESULTS: Of 103 oncology hcps who participated in the study, 75% were women. By hcp type, the most commonly reported professional groups were oncology nurse (40%), radiation therapist (9%), and pharmacist (6%). Of respondents, 75% reported providing direct care to cancer patients. More than half (69%) had spoken to a patient about cannabis in the preceding month, and 84% believed that they lacked sufficient knowledge about cannabis to make recommendations. Barriers such as monitoring the patient's use of cannabis (54%), prescribing an accurate dose (61%) or strain (53%), and having insufficient research (50%) were most commonly reported. More than half of hcps (53%) would be interested in receiving more information or training about the use of cannabis in oncology. CONCLUSIONS: The survey indicated that this group of oncology hcps believed that they lacked sufficient knowledge about cannabis to make recommendations to patients. In addition to that lack of knowledge, a number of notable barriers were reported, and more than half the hcps indicated interest in learning more about cannabis in the future.

McNamara, N., L. Dang, et al. (2020). "Thrombocytopenia in pediatric patients on concurrent cannabidiol and valproic acid." Epilepsia.

In January 2019, a new plant‐derived purified cannabidiol preparation, approved by the US Food and Drug Administration, became commercially available for patients ≥2 years old with Lennox‐Gastaut syndrome or Dravet syndrome. Among our patients who were prescribed the new cannabidiol formulation, we observed several cases of thrombocytopenia and therefore embarked on this study. We conducted a single‐center systematic chart review of all pediatric patients (<21 years old) who were prescribed cannabidiol from January to August 2019. We evaluated salient features of the patients’ epilepsy syndrome, age, concurrent medications, and surveillance laboratory results before and after cannabidiol initiation. Among 87 patients, nine (10%) developed thrombocytopenia (platelet nadir range = 17 000‐108 000) following initiation of cannabidiol. Each of these nine children was on combination therapy of cannabidiol with valproic acid. Whereas no children on cannabidiol without valproic acid (0/57) developed thrombocytopenia, nine of 23 treated with combination valproic acid and cannabidiol developed platelets < 110 000/µL (P < .0001). We report a novel and clinically important side effect of thrombocytopenia in one‐third of patients treated concurrently with cannabidiol and valproic acid. If this finding is confirmed, clinicians should perform close monitoring for thrombocytopenia when adding cannabidiol to a regimen that includes valproic acid.

Mecha, M., A. Feliú, et al. (2017). Chapter 93 - Cannabidiol and Multiple Sclerosis A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 893-904.

Abstract Cannabidiol (CBD), which constitutes up to 40% of the Cannabis sativa extract, have attracted special interest regarding putative therapeutic properties, excellent tolerability profile in humans, and lack of psychoactive actions. In animal models, CBD has been reported to act as an antiinflammatory, neuroprotective, and oligoprotective compound. The oromucosal spray administration of Sativex (a commercially available preparation containing CBD and Δ9-tetrahydrocannabinol, Δ9-THC) has been agreed for the treatment of pain and spasticity in multiple sclerosis (MS), a complex inflammatory disease with unknown etiology that courses with demyelination and neuronal injury in the brain and spinal cord. In this chapter, we will discuss about the different mechanisms of action of CBD, its beneficial effects on animal models of MS, and perspectives for human therapeutic treatment.

Meeker, J. D., E. Ayrian, et al. (2020). "Daring discourse - no: cannabinoids should not be used for acute postoperative pain management." Reg Anesth Pain Med **45**(7): 520-523.

As anesthesiologists and acute pain medicine specialists, we will care for patients in the perioperative period who use cannabinoids for chronic pain and/or marijuana recreationally. We will have to address difficult questions from patients regarding the potential applications for cannabinoids in acute pain management. While we must remain compassionate and understand our patients' desire to find relief from suffering using available non-opioid medications, we are ethically bound to do no harm and provide them with treatment options supported by the best available evidence. Today, we cannot support cannabinoids in the management of acute postoperative pain.

Meier, M. H., A. Caspi, et al. (2018). "Associations between adolescent cannabis use and neuropsychological decline: a longitudinal co-twin control study." Addiction **113**(2): 257-265.

Aims: This study tested whether adolescents who used cannabis or met criteria for cannabis dependence showed neuropsychological impairment prior to cannabis initiation and neuropsychological decline from before to after cannabis initiation. Design: A longitudinal co-twin control study. Setting and Participants: Participants were 1989 twins from the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative birth cohort of twins born in England and Wales from 1994 to 1995. Measurements: Frequency of cannabis use and cannabis dependence were assessed at age 18. Intelligence quotient (IQ) was obtained at ages 5, 12 and 18. Executive functions were assessed at age 18. Findings: Compared with adolescents who did not use cannabis, adolescents who used cannabis had lower IQ in childhood prior to cannabis initiation and lower IQ at age 18, but there was little evidence that cannabis use was associated with IQ decline from ages 12–18. For example, adolescents with cannabis dependence had age 12 and age 18 IQ scores that were 5.61 (t = −3.11, P = 0.002) and 7.34 IQ points (t = −5.27, P < 0.001) lower than adolescents without cannabis dependence, but adolescents with cannabis dependence did not show greater IQ decline from age 12–18 (t = −1.27, P = 0.20). Moreover, adolescents who used cannabis had poorer executive functions at age 18 than adolescents who did not use cannabis, but these associations were generally not apparent within twin pairs. For example, twins who used cannabis more frequently than their co-twin performed similarly to their co-twin on five of six executive function tests (Ps > 0.10). The one exception was that twins who used cannabis more frequently than their co-twin performed worse on one working memory test (Spatial Span reversed; β = −0.07, P = 0.036). Conclusions: Short-term cannabis use in adolescence does not appear to cause IQ decline or impair executive functions, even when cannabis use reaches the level of dependence. Family background factors explain why adolescent cannabis users perform worse on IQ and executive function tests.

Melchior, M., C. Bolze, et al. (2017). "Early cannabis initiation and educational attainment: is the association causal? Data from the French TEMPO study." International Journal of Epidemiology **46**(5): 1641-1650.

BackgroundAdolescent cannabis use has been reported to predict later educational attainment; however, results of past studies may be confounded by inappropriate control for factors that make some youths more likely to use cannabis precociously than others. We aimed to test the possibility of a causal relationship between early cannabis initiation and later academic achievement.MethodsAnalyses are based on data collected among TEMPO cohort study participants (France, 2009, n = 1103, 22–35 years). Participants were previously assessed in childhood (1991) and adolescence (1999); additionally, their parents had taken part in a longitudinal epidemiological cohort study (GAZEL). Early cannabis initiation was defined as use at age 16 or earlier. Educational attainment was defined as the completion of a high-school degree (‘Baccalauréat’). Early (up to and including age 16 years) and late (after age 16 years) cannabis-use initiators were compared with non-users using logistic regression models controlled for inverse probability weights (IPWs) of exposure calculated based on participants’ socio-demographic, juvenile and parental characteristics.ResultsIn age- and sex-adjusted analyses, early cannabis initiators were more likely than non-users to have low educational attainment [odds ratio (OR): 1.77, 95% confidence interval (CI) 1.22–2.55]. In IPWs-controlled analyses, this association somewhat decreased (OR: 1.64, 95% CI 1.13–2.40). Late cannabis initiators did not have lower educational attainment than non-users. Early cannabis use and educational attainment appeared more strongly associated in young women than in young men.ConclusionsEarly cannabis can cause low educational attainment. Youths who initiate cannabis use early require attention from addiction and education specialists to reduce their odds of poor long-term outcomes.

Mellis, C. (2018). "Cannabidiol for drug-resistant seizures in the Dravet syndrome." Journal of Paediatrics and Child Health **54**(1): 101-102.

Dravet syndrome (severe myoclonic epilepsy of infancy) is characterised by difficult-to-control seizures. Media reports and small clinical trials suggest that cannabidiol, a non-toxic extract of cannabis, can reduce seizure frequency. A recent multicentre randomised controlled trial of 120 children aged 2–18 years with Dravet syndrome supports its efficacy.[1] Over a 14-week period, children taking 20 mg/kg/day of cannabidiol had a 22.8% reduction (95% confidence interval 5.4–41.1) in seizure frequency compared to a 4-week baseline period. Median convulsive frequency fell from 12.4 to 5.9 per month on cannabidiol, while the placebo group had no change from baseline. No attempt was made to measure non-convulsive seizures (e.g. absences). Subjects took a median of three other anti-convulsant drugs during the trial. Adverse effects were common with cannabidiol, particularly somnolence, fatigue, loss of appetite, vomiting and diarrhoea. Eight patients in the cannabidiol group withdrew compared to one in the placebo group. Nevertheless, 62% of caregivers in the cannabidiol group felt the patient's overall condition had improved, using a validated global score, compared to 34% in the placebo group (P = 0.02). Unfortunately, the high rate of adverse events may have led to widespread loss of caregiver blinding, and the study is relatively short term. Nevertheless, the reduction in seizures is clinically relevant, and further longer-term randomised controlled trials are clearly warranted. GW Pharmaceuticals funded the study.

Meng, H., T. Dai, et al. (2020). "Cannabis and cannabinoids in cancer pain management." Curr Opin Support Palliat Care **14**(2): 87-93.

PURPOSE OF REVIEW: An increasing number of patients are turning to cannabis and cannabinoids for management of their palliative and nonpalliative cancer pain and other cancer-related symptoms. Canadians have a legal framework for access to medical cannabis, which provides a unique perspective in a setting lacking robust clinical evidence. This review seeks to delineate the role of cannabis and cannabinoids in cancer pain management and offers insight into the Canadian practice. RECENT FINDINGS: A cohort study using nabiximols on advanced cancer pain in patients already optimized on opioids, over 3 weeks, demonstrated improved average pain score. A large observational study of cancer patients using cannabis over 6 months demonstrated a decreased number of patients with severe pain and decreased opioid use, whereas the number of patients reporting good quality of life increased. SUMMARY: Good preclinical animal data and a large body of observational evidence point to the potential efficacy of cannabinoids for cancer pain management. However, there are relatively weak data pointing to clinical efficacy from clinical trial data to date. In Canada, the burgeoning cannabis industry has driven the population to embrace a medicine before clinical evidence. There remains a need for high-quality randomized controlled trials to properly assess the effectiveness and safety of medical cannabis, compared with placebo and standard treatments for cancer-related symptoms.

Miller, R. J. and R. E. Miller (2017). "Is cannabis an effective treatment for joint pain?" Clin Exp Rheumatol **35 Suppl 107**(5): 59-67.

Cannabis has been used to treat pain for thousands of years. However, since the early part of the 20th century, laws restricting cannabis use have limited its evaluation using modern scientific criteria. Over the last decade, the situation has started to change because of the increased availability of cannabis in the United States for either medical or recreational purposes, making it important to provide the public with accurate information as to the effectiveness of the drug for joint pain among other indications. The major psychotropic component of cannabis is Delta9-tetrahydrocannabinol (THC), one of some 120 naturally occurring phytocannabinoids. Cannabidiol (CBD) is another molecule found in herbal cannabis in large amounts. Although CBD does not produce psychotropic effects, it has been shown to produce a variety of pharmacological effects. Hence, the overall effects of herbal cannabis represent the collective activity of THC, CBD and a number of minor components. The action of THC is mediated by two major G-protein coupled receptors, cannabinoid receptor type 1 (CB1) and CB2, and recent work has suggested that other targets may also exist. Arachidonic acid derived endocannabinoids are the normal physiological activators of the two cannabinoid receptors. Natural phytocannabinoids and synthetic derivatives have produced clear activity in a variety of models of joint pain in animals. These effects are the result of both inhibition of pain pathway signalling (mostly CB1) and anti-inflammatory effects (mostly CB2). There are also numerous anecdotal reports of the effectiveness of smoking cannabis for joint pain. Indeed, it is the largest medical request for the use of the drug. However, these reports generally do not extend to regulated clinical trials for rheumatic diseases. Nevertheless, the preclinical and human data that do exist indicate that the use of cannabis should be taken seriously as a potential treatment of joint pain.

Min, J.-Y. and K.-B. Min (2018). "Marijuana use is associated with hypersensitivity to multiple allergens in US adults." Drug and Alcohol Dependence **182**: 74-77.

Background The recent legalization of marijuana use for both medical and recreational purposes in several states of the United Sates is expected to further increase the already high prevalence of marijuana use. Although allergic reactions are uncommon, the potential of marijuana use and cultivation to cause allergy should be considered. We aimed to investigate whether marijuana use is associated with the prevalence of sensitization to specific allergens. Methods A total of 2671 adults (aged 20–59 years) who participated in the 2005–2006 National Health and Nutrition Examination Survey were included. Participants completed a questionnaire on marijuana use and underwent sensitization tests to 19 specific allergens. Those who reported marijuana use for at least 1 day in the past 30 days were considered marijuana users. Results No difference was found in the history of allergy between marijuana users and non-users. Compared with marijuana non-users as a reference group, the adjusted odds ratio (AOR) of sensitization to a specific allergen among marijuana users was significantly greater for antibodies against the following: Alternaria alternata (AOR=1.67; 95% confidence interval (CI), 1.04−2.70), D. farinae (AOR=1.68; 95% CI, 1.27−2.22), D. pteronyssin (AOR=1.65; 95% CI, 1.32-2.06), ragweed (AOR=1.84; 95% CI, 1.30-2.59), rye grass (AOR=1.49; 95% CI, 1.12−1.97), Bermuda grass (AOR=1.55; 95% CI, 1.03−2.33), oak (AOR=1.76; 95% CI, 1.14−2.70), birch (AOR=2.09; 95% CI, 1.23−3.55), peanut (AOR=1.91; 95% CI, 1.25−2.92), and cat dander (AOR=1.51; 95% CI=1.13−2.03). Conclusions We provide preliminary findings to suggest that marijuana use is associated with sensitization to specific allergens, including molds, dust mites, plants, and cat dander.

Montero-Oleas, N., I. Arevalo-Rodriguez, et al. (2020). "Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews." BMC Complementary Medicine and Therapies **20**(1): 12.

Although cannabis and cannabinoids are widely used with therapeutic purposes, their claimed efficacy is highly controversial. For this reason, medical cannabis use is a broad field of research that is rapidly expanding. Our objectives are to identify, characterize, appraise, and organize the current available evidence surrounding therapeutic use of cannabis and cannabinoids, using evidence maps.

Mostafavi, M. and J. Gaitanis (2020). "Autism Spectrum Disorder and Medical Cannabis: Review & Clinical Experience." Seminars in Pediatric Neurology: 100833.

ABSTRACT Autism spectrum disorder (ASD) is a multifactorial, pervasive neurodevelopmental disorder defined by the core symptoms of significant impairment in social interaction and communication as well as restricted, repetitive patterns of behavior. In addition to these core behaviors, persons with ASD frequently have associated non-core behavioral disturbance (i.e. self-injury, aggression), as well as several medical comorbidities. Currently, no effective treatment exists for the core symptoms of ASD. This review reports the available pre-clinical and clinical data regarding the use of cannabis and cannabidiol (CBD) in the treatment of core symptoms, non-core symptoms and comorbidities associated with ASD. Additionally, we describe our clinical experience working with children and young adults with ASD who have used cannabis or CBD. At present, pre-clinical and clinical data suggest a potential for therapeutic benefit amongst some persons with ASD and that it is overall well tolerated. Further research is required to better identify patients who may benefit from treatment without adverse effects.

Mouhamed, Y., A. Vishnyakov, et al. (2018). "Therapeutic potential of medicinal marijuana: an educational primer for health care professionals." Drug Health Patient Saf 10: 45-66.

With the proposed Canadian July 2018 legalization of marijuana through the Cannabis Act, a thorough critical analysis of the current trials on the efficacy of medicinal marijuana (MM) as a treatment option is necessary. This review is particularly important for primary care physicians whose patients may be interested in using MM as an alternative therapy. In response to increased interest in MM, Health Canada released a document in 2013 for general practitioners (GPs) as an educational tool on the efficacy of MM in treating some chronic and acute conditions. Although additional studies have filled in some of the gaps since the release of the Health Canada document, conflicting and inconclusive results continue to pose a challenge for physicians. This review aims to supplement the Health Canada document by providing physicians with a critical yet concise update on the recent advancements made regarding the efficacy of MM as a potential therapeutic option. An update to the literature of 2013 is important given the upcoming changes in legislation on the use of marijuana. Also, we briefly highlight the current recommendations provided by Canadian medical colleges on the parameters that need to be considered prior to authorizing MM use, routes of administration as well as a general overview of the endocannabinoid system as it pertains to cannabis. Lastly, we outline the appropriate medical conditions for which the authorization of MM may present as a practical alternative option in improving patient outcomes as well as individual considerations of which GPs should be mindful. The purpose of this paper is to offer physicians an educational tool that provides a necessary, evidence-based analysis of the therapeutic potential of MM and to ensure physicians are making decisions on the therapeutic use of MM in good faith.

Mohammadpour, F., S. N. Ostad, et al. (2017). "Anti-invasion Effects of Cannabinoids Agonist and Antagonist on Human Breast Cancer Stem Cells." Iranian Journal of Pharmaceutical Research **16**(4): 1479-1486.

Studies show that cancer cell invasion or metastasis is the primary cause of death in malignancies including breast cancer. The existence of cancer stem cells (CSCs) in breast cancer may account for tumor initiation, progression, and metastasis. Recent studies have reported different effects of cannabinoids on cancer cells via CB1 and CB2 cannabinoid receptors. In the present study, the effects of ACEA (a selective CB1 receptor agonist) and AM251 (a selective CB1 antagonist) on CSCs and their parental cells were investigated. Breast CSCs derived from MDA-MB-231 cell line were sorted and characterized with CD44+/CD24-/low/ESA+ phenotype. It was observed that ACEA decreased CD44+/CD24-/low/ESA+ cancer stem cell invasiveness. Conversely, AM251 increased the invasion by more than 20% (at the highest concentrations) in both MDA-MB-231 and CSCs. Our results did not show any correlation between reduced invasion and cytotoxic effects of the drug. Since one of the main cancer recurrence factors is anti-cancer drugs fail to inhibit CSC population, this observation would be useful for cancer treatment. [ABSTRACT FROM AUTHOR]

Monte, A. A., S. K. Shelton, et al. (2019). "Acute Illness Associated With Cannabis Use, by Route of Exposure: An Observational Study." Annals of Internal Medicine 170(8): 531-537.

Little is known about the relative harms of edible and inhalable cannabis products.To describe and compare adult emergency department (ED) visits related to edible and inhaled cannabis exposure.Chart review of ED visits between 1 January 2012 and 31 December 2016.A large urban academic hospital in Colorado.Adults with ED visits with a cannabis-related International Classification of Diseases, Ninth or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM), code.Patient demographic characteristics, route of exposure, dose, symptoms, length of stay, disposition, discharge diagnoses, and attribution of visit to cannabis.There were 9973 visits with an ICD-9-CM or ICD-10-CM code for cannabis use. Of these, 2567 (25.7%) visits were at least partially attributable to cannabis, and 238 of those (9.3%) were related to edible cannabis. Visits attributable to inhaled cannabis were more likely to be for cannabinoid hyperemesis syndrome (18.0% vs. 8.4%), and visits attributable to edible cannabis were more likely to be due to acute psychiatric symptoms (18.0% vs. 10.9%), intoxication (48% vs. 28%), and cardiovascular symptoms (8.0% vs. 3.1%). Edible products accounted for 10.7% of cannabis-attributable visits between 2014 and 2016 but represented only 0.32% of total cannabis sales in Colorado (in kilograms of tetrahydrocannabinol) during that period.Retrospective study design, single academic center, self-reported exposure data, and limited availability of dose data.Visits attributable to inhaled cannabis are more frequent than those attributable to edible cannabis, although the latter is associated with more acute psychiatric visits and more ED visits than expected.Colorado Department of Public Health and Environment.

Morrison, G., J. Crockett, et al. (2019). "A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects." Clin Pharmacol Drug Dev.

GW Pharmaceuticals' formulation of highly purified cannabidiol oral solution is approved in the United States for seizures associated with Lennox-Gastaut and Dravet syndromes in patients aged >/=2 years, for which clobazam, stiripentol, and valproate are commonly used antiepileptic drugs. This open-label, fixed-sequence, drug-drug interaction, healthy volunteer trial investigated the impact of cannabidiol on steady-state pharmacokinetics of clobazam (and N-desmethylclobazam), stiripentol, and valproate; the reciprocal effect of clobazam, stiripentol, and valproate on cannabidiol and its major metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]); and cannabidiol safety and tolerability when coadministered with each antiepileptic drug. Concomitant cannabidiol had little effect on clobazam exposure (maximum concentration [Cmax ] and area under the concentration-time curve [AUC], 1.2-fold), N-desmethylclobazam exposure increased (Cmax and AUC, 3.4-fold), stiripentol exposure increased slightly (Cmax , 1.3-fold; AUC, 1.6-fold), while no clinically relevant effect on valproate exposure was observed. Concomitant clobazam with cannabidiol increased 7-OH-CBD exposure (Cmax , 1.7-fold; AUC, 1.5-fold), without notable 7-COOH-CBD or cannabidiol increases. Stiripentol decreased 7-OH-CBD exposure by 29% and 7-COOH-CBD exposure by 13%. There was no effect of valproate on cannabidiol or its metabolites. Cannabidiol was moderately well tolerated, with similar incidences of adverse events reported when coadministered with clobazam, stiripentol, or valproate. There were no deaths, serious adverse events, pregnancies, or other clinically significant safety findings.

Nada, S. A., O. M. E. Abdel-Salam, et al. (2017). Chapter 53 - Cannabis and Hepatic Injury A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 505-516.

Abstract Elevated serum liver enzymes are a frequent finding among chronic users of cannabis preparations. Smoking cannabis is common among patients with chronic liver disease due to hepatitis C virus. In these patients, cannabis has been implicated both in the progression of fibrosis and fatty liver, and in increasing the outcome of antiviral therapy. Cannabis use in liver transplant recipients is not uncommon, but the exact adverse consequences are yet to be determined. Data from animal studies suggested different role for cannabinoid receptors, with a beneficial hepatoprotective effect for cannabinoid receptor 2 (CB2) stimulation, as opposed to a fibrogenic and steatogenic role mediated by cannabinoid receptors 1 (CB1). These data indicate a possible role for selective CB1 antagonists or CB2 agonists in treating liver fibrosis, fatty liver disease, and in ameliorating the hemodynamic changes and cardiomyopathy in liver cirrhosis.

Nader, D. A. and Z. M. Sanchez (2018). "Effects of regular cannabis use on neurocognition, brain structure, and function: a systematic review of findings in adults." The American Journal of Drug and Alcohol Abuse **44**(1): 4-18.

ABSTRACTBackground: Cannabis is the most used illicit drug worldwide. The long-standing consequences for the central nervous system associated with frequent cannabis use have not been well delineated and should be determined. Objective: To review recent studies on the effects of regular cannabis use regarding its effects on cognition, brain structure, and function in adults. Methods: A systematic literature review was conducted by performing electronic searches in the PubMed, LILACS, and SciELO databases (2010?2016). The initial search identified 898 records. They were evaluated for relevance according to the inclusion and exclusion criteria and 56 studies were included. Results: The neuropsychological studies provide evidence for subtle cognitive deficits at least 7 days after heavy cannabis use. The structural neuroimaging studies show growing evidence of abnormalities in hippocampus volume and gray matter density of cannabis users relative to controls; however, morphological changes in other brain regions are more controversial. The functional neuroimaging studies suggest an altered pattern of brain activity associated with cannabis use. Conclusion: Although there are several limitations for study comparison and substantial heterogeneity in the findings, the present review suggests that regular cannabis use is associated with mild cognitive changes in addition to structural and functional alterations in the brain in adults. The morphological alterations could ultimately affect brain organization and function, but the associated time course for neuronal recovery as well as the real impact on cognitive functioning remain unknown. Also, it is still unclear whether the identified alterations are as a consequence of or precede cannabis use.

Nathan, R. A., C. T. Mupamombe, et al. (2019). "Use of medical cannabis in treating anorexia and nausea in elderly cancer patients." Journal of Clinical Oncology 37(31\_suppl): 124-124.

Background: The use of medical cannabis (MC) in cancer symptom treatment has been increasing. Since its legalization is limited to select states, there are few clinical trials that have studied the effectiveness and safety of MC, and even fewer studies in the elderly patient population. Given this, we aimed to evaluate the effects of MC on nausea, appetite, and body mass index (BMI) of elderly cancer patients. Methods: We conducted a retrospective chart review of patients age 65 and older prescribed MC in the year 2018 in an outpatient palliative care clinic at a comprehensive cancer center. Nausea and appetite were measured by numerical rating (0-10) and BMI was recorded with data collected at consecutive clinic visits before and after MC use. Results: Eight-three patients aged 65 and over were included in our analysis. Half of patients were age 65-70, while 12% were age 76 or older. More than half were male (58%) and Caucasian (92%). For patients with anorexia or nausea, 58% had previously used cannabis. For nausea, 58% were prescribed ondansetron, 53% were prescribed prochlorperazine or metoclopramide, and 20% were prescribed olanzapine. For anorexia, 24% were prescribed mirtazapine, 6% were prescribed dronabinol, and 1% were prescribed megestrol. The majority of patients used oil (64%), with one-third using vape (33%) and fewer using pill (17%) and powder (5%). Patients primarily used high THC (50%) or equal THC:CBD (45%) formulations initially, with only 7% using high CBD products. The median nausea and anorexia trended towards improvement, though neither was significant (delta nausea = 0.1, p = 0.81) nor anorexia score (delta anorexia = 0.7, p = 0.69). BMI worsened despite MC use (delta BMI 1.9, p < 0.001). Conclusions: In this study of elderly patients with cancer prescribed MC, more than half had previously used cannabis. Two-thirds of patients with anorexia were using MC first-line for appetite stimulation. The majority of patients used oil, with vape next most commonly used, and the vast majority of patients using high THC or equal THC:CBD initially. Use of MC was not associated with a significant improvement in nausea nor anorexia, and BMI significantly decreased despite MC use.

Nenert, R., J. B. Allendorfer, et al. (2020). "Cannabidiol normalizes resting-state functional connectivity in treatment-resistant epilepsy." Epilepsy & Behavior **112**: 107297.

Objective Resting-state (rs) network dysfunction is a contributing factor to treatment resistance in epilepsy. In treatment-resistant epilepsy (TRE), pharmacological and nonpharmacological therapies have been shown to improve such dysfunction. In this study, our goal was to prospectively evaluate the effect of highly purified plant-derived cannabidiol (CBD; Epidiolex®) on rs functional magnetic resonance imaging (fMRI) functional connectivity (rs-FC). We hypothesized that CBD would change and potentially normalize the rs-FC in TRE. Methods Twenty-two of 27 participants with TRE completed all study procedures including longitudinal pre-/on-CBD rs-fMRI (8M/14F, mean age = 36.2 ± 15.9 years, TRE duration = 18.3 ± 12.6 years); there were no differences in age (p = 0.99) or sex (p = 0.15) between groups. Assessments collected included seizure frequency (SF), Chalfont Seizure Severity Scale (CSSS), Columbia Suicide Severity Rating Scale (C-SSRS), Adverse Events Profile (AEP), and Profile of Mood States (POMS). Twenty-three healthy controls (HCs) received rs-fMRI and POMS once. Results Participants with TRE showed average decrease of 71.7% in SF (p < 0.0001) and improved CSSS, AEP, and POMS confusion, depression, and fatigue subscores (all p < 0.05) on-CBD with POMS scores becoming similar to those of HCs. Paired t-tests showed significant pre-/on-CBD changes in rs-FC in cerebellum, frontal areas, temporal areas, hippocampus, and amygdala with some of them correlating with improvement in behavioral measures. Significant differences in rs-FC between pre-CBD and HCs were found in cerebellum, frontal, and occipital regions. After controlling for changes in SF with CBD, these differences were no longer present when comparing on-CBD to HCs. Significance This study indicates that highly purified CBD modulates and potentially normalizes rs-FC in the epileptic brain. This effect may underlie its efficacy. This study provides Class III evidence for CBD's normalizing effect on rs-FC in TRE.

Newton, M. and D. W. Newton (2020). "Cannabidiol or CBD Oil: Help, Hope, and Hype for Psychiatric and Neurologic Conditions." J Am Psychiatr Nurses Assoc **26**(5): 447-457.

OBJECTIVE: This article presents proven, promising, and potential therapeutic uses for cannabidiol (CBD) in the treatment of psychiatric and neurologic conditions and diseases. It presents popular, but scientifically unproven health and therapeutic claims of CBD supporting the beneficial homeostatic effects of the intrinsic or endogenous cannabinoid system. It includes a review of cannabinoid pharmacology; it compares properties and the legal status of CBD and THC (delta 9-tetrahydrocannabinol) as well as the hemp and marijuana varieties of Cannabis, and it reviews the historic 2018 U.S. Food and Drug Administration approval of Epidiolex, an oral solution of cannabidiol for two rare treatment-resistant childhood epilepsies, as the first Cannabis-derived drug. METHOD: We reviewed literature on cannabidiol, CBD, the endocannabinoid neuropharmacology system, and hemp and marijuana varieties of Cannabis sativa. RESULTS: The proven and promising medical uses and deficiencies of unproven health claims for CBD, legal implications for Cannabis-derived drugs, and comparisons of CBD and THC and hemp and marijuana are summarized objectively with pertinent references. CONCLUSION: CBD and CBD and THC combinations have potential to provide safe, effective therapy for several psychiatric and neurologic conditions and diseases. However, such achievement will require a uniform standard of CBD purity and strength, and corroboration from adequately large and rigorously controlled clinical research studies.

Nielsen, S., R. Germanos, et al. (2018). "The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews." Current Neurology and Neuroscience Reports **18**(2): 8.

Pharmaceutical cannabinoids such as nabiximols, nabilone and dronabinol, and plant-based cannabinoids have been investigated for their therapeutic potential in treating multiple sclerosis (MS) symptoms. This review of reviews aimed to synthesise findings from high quality systematic reviews that examined the safety and effectiveness of cannabinoids in multiple sclerosis. We examined the outcomes of disability and disability progression, pain, spasticity, bladder function, tremor/ataxia, quality of life and adverse effects.

Nordmann, S., A. Vilotitch, et al. (2018). "Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH)." Journal of Viral Hepatitis **25**(2): 171-179.

Liver steatosis is common in human immunodeficiency virus (HIV)-hepatitis C virus (HCV)-co-infected patients. Some recent studies have found that cannabis use is negatively associated with insulin resistance in the general population and in HIV-HCV-co-infected patients. Given the causal link between insulin resistance and steatosis, we hypothesized that cannabis use has a positive impact on steatosis. Therefore, we aimed to study whether cannabis use in this population was associated with a reduced risk of steatosis, measured by ultrasound examination. ANRS CO13-HEPAVIH is a French nationwide multicentre cohort of HIV-HCV-co-infected patients. Medical and socio-behavioural data from clinical follow-up visits and annual self-administered questionnaires were prospectively collected. A cross-sectional analysis was conducted using data from the first visit where both ultrasound examination data for steatosis (positive or negative diagnosis) and data on cannabis use were available. A logistic regression model was used to evaluate the association between cannabis use and steatosis. Among study sample patients (n = 838), 40.1% had steatosis. Fourteen per cent reported daily cannabis use, 11.7% regular use and 74.7% no use or occasional use (“never or sometimes”). Daily cannabis use was independently associated with a reduced prevalence of steatosis (adjusted odds ratio [95% CI] = 0.64 [0.42;0.99]; P = .046), after adjusting for body mass index, hazardous alcohol consumption and current or lifetime use of lamivudine/zidovudine. Daily cannabis use may be a protective factor against steatosis in HIV-HCV-co-infected patients. These findings confirm the need for a clinical evaluation of cannabis-based pharmacotherapies in this population. Eudract.ema.europa.eu number, DGS050367.

Nugent, S. M., B. J. Yarborough, et al. (2018). "Patterns and correlates of medical cannabis use for pain among patients prescribed long-term opioid therapy." General Hospital Psychiatry **50**: 104-110.

Objective Little is known about co-occurring long-term opioid therapy (LTOT) and medical cannabis use. We compared characteristics of patients prescribed LTOT who endorsed using medical cannabis for pain to patients who did not report cannabis use. Method Participants (n=371) prescribed LTOT completed self-report measures about pain, substance use, and mental health. Results Eighteen percent of participants endorsed using medical cannabis for pain. No significant differences were detected on pain-related variables, depression, or anxiety between those who endorsed medical cannabis use and those who did not. Medical cannabis users had higher scores of risk for prescription opioid misuse (median=17.0 vs. 11.5, p<0.001), rates of hazardous alcohol use (25% vs. 16%, p<0.05), and rates of nicotine use (42% vs. 26%, p=0.01). Multivariable analyses indicated that medical cannabis use was significantly associated with risk of prescription opioid misuse (β=0.17, p=0.001), but not hazardous alcohol use (aOR=1.96, 95% CI=0.96–4.00, p=0.06) or nicotine use (aOR=1.61, 95% CI=0.90–2.88, p=0.11). Conclusion There are potential risks associated with co-occurring LTOT and medical cannabis for pain. Study findings highlight the need for further clinical evaluation in this population. Future research is needed to examine the longitudinal impact of medical cannabis use on pain-related and substance use outcomes.

O'Brien, M. and J. J. McDougall (2018). "Cannabis and joints: scientific evidence for the alleviation of osteoarthritis pain by cannabinoids." Curr Opin Pharmacol 40: 104-109.

Cannabis has been used for millennia to treat a multitude of medical conditions including chronic pain. Osteoarthritis (OA) pain is one of the most common types of pain and patients often turn to medical cannabis to manage their symptoms. While the majority of these reports are anecdotal, there is a growing body of scientific evidence which supports the analgesic potential of cannabinoids to treat OA pain. OA pain manifests as a combination of inflammatory, nociceptive, and neuropathic pain, each requiring modality-specific analgesics. The body's innate endocannabinoid system (ECS) has been shown to ameliorate all of these pain subtypes. This review summarizes the components of the ECS and details the latest research pertaining to plant-based and man-made cannabinoids for the treatment of OA pain. Recent pre-clinical evidence supporting a role for the ECS to control OA pain is described as well as current clinical evidence of the efficacy of cannabinoids for treating OA pain in mixed patient populations.

O’Hearn, S., P. Diaz, et al. (2017). "Modulating the endocannabinoid pathway as treatment for peripheral neuropathic pain: a selected review of preclinical studies." Annals of Palliative Medicine: S209-S214.

Chemotherapy-induced neuropathic pain is a distressing and commonly occurring side effect of many commonly used chemotherapeutic agents, which in some cases may prevent cancer patients from being able to complete their treatment. Cannabinoid based therapies have the potential to manage or even prevent pain associated with this syndrome. Pre-clinical animal studies that investigate the modulation of the endocannabinoid system (endogenous cannabinoid pathway) are being conducted to better understand the mechanisms behind this phenomenon. Five recent pre-clinical studies identified from Medline published between 2013 and 2016 were selected for review. All studies evaluated the effect of small-molecule agonists or antagonists on components of the endocannabinoid system in rats or mice, using cisplatin or paclitax-el-induced allodynia as a model of chemotherapy-induced neuropathic pain. Activation of the cannabinoid receptor-2 (CB-2) receptor by AM1710 blocked paclitaxel-induced mechanical and cold allodynia in one study. Four studies investigating the activation of both cannabinoid receptor-1 (CB-1) and CB-2 receptors by dual-agonists (WIN55,21 and CP55,940), or by the introduction of inhibitors of endocannabinoid metabolisers (URB597, URB937, JZL184, and SA-57) showed reduction of chemotherapy-induced al-lodynia. In addition, their results suggest that anti-allodynic effects may also be mediated by additional receptors, including TRPV1 and 5-hydroxytryptamine (5-HT 1A ). Pre-clinical studies demon-strate that the activation of endocannabinoid CB-1 or CB-2 receptors produces physiological effects in animal models, namely the reduction of chemotherapy-induced allodynia. These studies also provide in-sight into the biological mechanism behind the therapeutic utility of cannabis compounds in managing chemotherapy-induced neuropathic pain, and provide a basis for the conduct of future clinical studies in patients of this population.

O’Keefe, E. L., T. M. Peterson, et al. (2020). "Reevaluating America’s Latest Pharmaceutical Trend: The Cardiovascular Risk of Cannabis." Current Opinion in Psychology.

For the first time in the history of the modern era smoking tobacco is not the most popular inhaled product. After a flurry of legislature, cannabis has come to the forefront of both medicinal and recreational drug use. A confluence of evidence suggests, however, that marijuana consumption may confer a particularly worrisome cardiovascular risk profile. While combustible forms still contain many of the same harmful chemicals found in tobacco such as aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and nitric oxide, some in even greater concentrations than tobacco, edible preparations have been evidenced to cause more cardiovascular-related emergency department visits. Importantly, this body of evidence suggests that cannabis use may be placing a younger, healthier population at risk of suffering major cardiovascular accidents particularly in the moments immediately following consumption. With males in their 30’s apparently bearing the brunt of this burden, cannabis consumption has been associated with an increase in ischemic stroke—a blockage in the cerebral or cerebellar vasculature—and almost a fivefold increase in myocardial infarction. THC containing compounds have also been linked to vascular complications ranging from mild plaques to total arterial occlusion resulting in claudication, rest pain, ischemic ulceration and gangrene—recently termed cannabis arteritis. While this research remains in a nascent stage, marijuana consumption seems to be predisposing a youthful, traditionally low health risk cohort to a variety of major adverse cardiovascular events.

O’Neill, A., L. Annibale, et al. (2020). "O5.2. CBD MODULATION OF HIPPOCAMPAL GLUTAMATE IN PSYCHOSIS." Schizophrenia Bulletin **46**(Suppl 1): S11-S11.

BACKGROUND: Emerging evidence supports the antipsychotic effect of cannabidiol (CBD), a non-intoxicating component of cannabis, in people with psychosis. However, how CBD might exert its antipsychotic effect remains unclear. While current antipsychotic medications typically target the dopaminergic neurotransmitter system, preclinical findings suggest that CBD may directly or indirectly affect multiple distinct modes of neural signalling, including both glutamate and dopamine. However, no study has as yet investigated the effect of CBD on brain glutamate levels in patients with psychosis as a potential mechanism underlying its antipsychotic effects. METHODS: We investigated the effects of a single oral dose of CBD (600mg), compared to a matched placebo, in patients within 5 years of onset of psychosis, using a double-blind, randomized, placebo-controlled, repeated-measures, within-subject cross-over design, with at least a one-week interval between scans to allow washout of CBD. After drug administration, 13 patients (mean age 27.73, 66.7% male) were scanned using proton magnetic resonance spectroscopy to measure left hippocampal glutamate levels. Symptom severity was assessed using the Positive and Negative syndrome scale (PANSS) 60mins before drug administration (T1, pre scan), and 270mins after drug administration (T2, post scan). Effects of CBD on left hippocampal glutamate levels, symptoms, and correlations between hippocampal glutamate and symptoms were investigated. RESULTS: Compared to placebo, there was a significant increase in left hippocampal glutamate in the psychosis patients under CBD treatment (z= -1.80; p=0.035). Under placebo treatment, change in positive psychotic symptoms (as indexed using the T1 minus T2 PANSS positive symptoms subscale scores) was directly correlated with left hippocampal glutamate levels (rho= 0.69, p=0.004), such that symptoms increased as hippocampal glutamate levels decreased. This significant relationship was not observed under the CBD treatment (rho= 0.102, p=0.72). DISCUSSION: This suggests that positive psychotic symptoms may be driven by abnormal hippocampal glutamate concentration, which is sensitive to modulation by CBD. These findings are in keeping with the purported antipsychotic effects of CBD in psychosis, and provide novel insight into the neurochemical interactions underlying these effects.

Oberbarnscheidt, T. and N. Miller (2020). "The Impact of Cannabidiol on Psychiatric and Medical Conditions." Journal of Clinical Medicine Research **12**: 393-403.

Cannabidiol (CBD) is a substance chemically derived from Cannabis sativa and discussed to be non-psychoactive. According to the FDA, marijuana is classified as a schedule I substance; however, hemp which is defined as extracts from marijuana including cannabinoids containing less than 0.3% tetrahydrocannabinol (THC), is excluded from that controlled substance act and available at local convenience stores in the US as it is seen as an herbal supplement. CBD is purported to be used for various medical and psychiatric conditions: depression, anxiety, post-traumatic stress disorder, Alzheimer's or other cognitive illnesses as well as pain. There is also a new trend to use CBD for the treatment of opioid use disorder. The one CBD product on the market that is FDA approved for the treatment of childhood epilepsy forms Dravet and Lennox-Gastaut syndromes is available under the name Epidiolex. There is a significant difference between this medication and the over-the-counter CBD products that contain very inconsistent strengths of CBD, if they contain it at all, and vary in percentage even from sample to sample. Frequently the so-called CBD products are not containing any CBD at all, but mostly containing THC. This article is a systematic review of literature reviewing the available clinical data on CBD, for use in various medical and psychiatric conditions with focus on a review of the pharmacology and toxicity. Resources used were ORVID, PubMed, MEDLINE, PsychINFO, EMBASE with keywords CBD, cannabidiol, hemp and cannabinoids.

Okusanya, B. O., I. O. Asaolu, et al. (2020). "Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review." Systematic reviews **9**(1): 167-167.

BACKGROUND: Medical cannabis (MC) is currently being used as an adjunct to opiates given its analgesic effects and potential to reduce opiate addiction. This review assessed if MC used in combination with opioids to treat non-cancer chronic pain would reduce opioid dosage. METHODS: Four databases-Ovid (Medline), Psyc-INFO, PubMed, Web of Science, and grey literature-were searched to identify original research that assessed the effects of MC on non-cancer chronic pain in humans. Study eligibility included randomized controlled trials, controlled before-and-after studies, cohort studies, cross-sectional studies, and case reports. All databases were searched for articles published from inception to October 31, 2019. Cochrane's ROBINS-I tool and the AXIS tool were used for risk of bias assessment. PRISMA guidelines were followed in reporting the systematic review. RESULTS: Nine studies involving 7222 participants were included. There was a 64-75% reduction in opioid dosage when used in combination with MC. Use of MC for opioid substitution was reported by 32-59.3% of patients with non-cancer chronic pain. One study reported a slight decrease in mean hospital admissions in the past calendar year (P = .53) and decreased mean emergency department visits in the past calendar year (P = .39) for patients who received MC as an adjunct to opioids in the treatment of non-cancer chronic pain compared to those who did not receive MC. All included studies had high risk of bias, which was mainly due to their methods. CONCLUSIONS: While this review indicated the likelihood of reducing opioid dosage when used in combination with MC, we cannot make a causal inference. Although medical cannabis' recognized analgesic properties make it a viable option to achieve opioid dosage reduction, the evidence from this review cannot be relied upon to promote MC as an adjunct to opioids in treating non-cancer chronic pain. More so, the optimal MC dosage to achieve opioid dosage reduction remains unknown. Therefore, more research is needed to elucidate whether MC used in combination with opioids in the treatment of non-cancer chronic pain is associated with health consequences that are yet unknown. SYSTEMATIC REVIEW REGISTRATION: This systematic review was not registered.

Orsolini, L., S. Chiappini, et al. (2019). "Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review." Medicina (Kaunas) 55(9).

BACKGROUND AND OBJECTIVES: Post-traumatic stress disorder (PTSD) is a common psychiatric disorder resulting from a traumatic event, is manifested through hyperarousal, anxiety, depressive symptoms, and sleep disturbances. Despite several therapeutic approaches being available, both pharmacological and psychological, recently a growing interest has developed in using cannabis and synthetic cannabinoids stems from their consideration as more efficient and better tolerated alternatives for the treatment of this condition. The present paper aims to evaluate the clinical and therapeutic potentials of medical cannabis and synthetic cannabinoids in treating PTSD patients. METHODS: A systematic electronic search was performed, including all papers published up to May 2019, using the following keywords (((cannabis[Title/Abstract]) OR (synthetic cannabinoids [Title/Abstract])) AND ((PTSD[Title/Abstract]) OR (Posttraumatic stress disorder[Title/Abstract]))) for the topics 'Cannabis', 'Synthetic Cannabinoids', 'PTSD', and MESH terms, on the PubMed, Cochrane Library, and Web of Science online databases. For data gathering purposes, PRISMA guidelines were followed. Results were organized into two groups, considering cannabis and synthetic cannabinoids as different therapeutic approaches for PTSD. RESULTS: Present data show that cannabis and synthetic cannabinoids, both acting on the endocannabinoids system, may have a potential therapeutic use for improving PTSD symptoms, e.g., reducing anxiety, modulating memory-related processes, and improving sleep. CONCLUSIONS: Even though the current literature suggests that cannabis and synthetic cannabinoids may have a role in the treatment of PTSD, there is currently limited evidence regarding their safety and efficacy. Therefore, additional research is needed in order to better understand the effectiveness and therapeutic usage of these drug classes and monitor their safety.

Pacheco-Colón, I., S. Coxe, et al. (2018). "Is Cannabis Use Associated with Various Indices of Motivation among Adolescents?" Substance Use & Misuse **53**(7): 1158-1169.

ABSTRACTDecreased motivation is often noted as a consequence of cannabis use (CU). Previous work has yielded mixed findings, relied mostly on adult samples, and varied to the extent that it accounted for potential confounds. This study examines associations between CU and several motivation indices among adolescents. We hypothesized that regular cannabis users would report lower motivation than light users, and that greater lifetime and past 30-day CU amounts would be associated with decreased motivation. Participants were 79 adolescents, ages 14?18, classified as recent regular cannabis users (n = 36) or light users (n = 43). Frequency and amount of substance use were assessed across participants? lifetime and during the past 30 days. Motivation was measured through the Apathy Evaluation Scale and Motivation and Engagement Scale. To examine associations between CU and our motivation indices, we conducted a series of two-step hierarchical multiple regressions. Variables found to correlate with any motivation measure were entered on step 1 (e.g., mental health, other substance use) and the relevant CU variable was entered on step 2. After controlling for confounds, no significant differences were observed between regular and light users on any motivation index, p > .01. Similarly, no associations between motivation and lifetime or past 30-day CU amount were observed, p > .01. Our findings do not support a link between reduced motivation and CU among adolescents after controlling for relevant confounds. Future studies will examine the levels of CU which influence motivation in adolescents, and the conditions under which this link becomes manifest.

Pacher, P., S. Steffens, et al. (2017). "Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly." Nature Reviews Cardiology **15**: 151.

Dysregulation of the endogenous lipid mediators endocannabinoids and their G-protein-coupled cannabinoid receptors 1 and 2 (CB1R and CB2R) has been implicated in a variety of cardiovascular pathologies. Activation of CB1R facilitates the development of cardiometabolic disease, whereas activation of CB2R (expressed primarily in immune cells) exerts anti-inflammatory effects. The psychoactive constituent of marijuana, Δ9-tetrahydrocannabinol (THC), is an agonist of both CB1R and CB2R, and exerts its psychoactive and adverse cardiovascular effects through the activation of CB1R in the central nervous and cardiovascular systems. The past decade has seen a nearly tenfold increase in the THC content of marijuana as well as the increased availability of highly potent synthetic cannabinoids for recreational use. These changes have been accompanied by the emergence of serious adverse cardiovascular events, including myocardial infarction, cardiomyopathy, arrhythmias, stroke, and cardiac arrest. In this Review, we summarize the role of the endocannabinoid system in cardiovascular disease, and critically discuss the cardiovascular consequences of marijuana and synthetic cannabinoid use. With the legalization of marijuana for medicinal purposes and/or recreational use in many countries, physicians should be alert to the possibility that the use of marijuana or its potent synthetic analogues might be the underlying cause of severe cardiovascular events and pathologies.

Pane, C. and F. Saccà (2020). "The use of medical grade cannabis in Italy for drug-resistant epilepsy: a case series." Neurol Sci **41**(3): 695-698.

In Italy, medical grade cannabis (MGC) can be prescribed for different medical conditions, including drug-resistant epilepsy (DRE), once standard and approved therapies have failed, or caused non-tolerable side effects. Here, we present a retrospective case series report of five patients with DRE who started therapy with MGC. Authorized ISO 9001:2008 pharmacies prepared MGC according to Italian laws. Olive oil extracts (OOEs) were prepared following standard extraction protocols, and cannabinoids were measured on each OOE to check for successful extraction.After treatment with MGC, all patients reported a reduction in seizure frequency and severity, and some reported improved mood, sleep quality, and general well-being without relevant side effects. Despite the small sample size and open-label nature of the data, we show that MGC may be successfully used to treat DRE. This is especially true when considering that no valid therapeutic option exists for these patients and that MGC was extremely well tolerated.

Panozzo, S., B. Le, et al. (2020). "Who is asking about medicinal cannabis in palliative care?" Intern Med J **50**(2): 243-246.

Following legislative changes in the availability and prescribing of medicinal cannabis in Australia, we sought to understand prospectively the nature of information seeking and requests for medicinal cannabis in consultations between palliative care clinicians and patients with cancer. The 104 discussions were overwhelmingly initiated by patients and carers (93%) and were for a variety of symptoms, reflecting high levels of patient interest in the use of medicinal cannabis in cancer.

Patra, P. H., E. Serafeimidou-Pouliou, et al. (2020). "Cannabidiol improves survival and behavioural co-morbidities of Dravet syndrome in mice." British journal of pharmacology **177**(12): 2779-2792.

BACKGROUND AND PURPOSE: Dravet syndrome is a severe, genetic form of paediatric epilepsy associated with premature mortality and co-morbidities such as anxiety, depression, autism, motor dysfunction and memory deficits. Cannabidiol is an approved anticonvulsive drug in the United States and Europe for seizures associated with Dravet syndrome in patients 2 years of age and older. We investigated its potential to prevent premature mortality and improve associated co-morbidities. EXPERIMENTAL APPROACH: The efficacy of sub-chronic cannabidiol administration in two mouse models of Dravet syndrome was investigated. The effect of cannabidiol on neonatal welfare and survival was studied using Scn1a(-/-) mice. We then used a hybrid, heterozygote Scn1a(+/-) mouse model to study the effect of cannabidiol on survival and behavioural co-morbidities: motor deficits (rotarod and static-beam test), gait abnormality (gait test), social anxiety (social interaction test), anxiety-like (elevated plus maze) and depressive-like behaviours (sucrose preference test) and cognitive impairment (radial arm maze test). KEY RESULTS: In Scn1a(-/-) mice, cannabidiol increased survival and delayed worsening of neonatal welfare. In Scn1a(+/-) mice, chronic cannabidiol administration did not show any adverse effect on motor function and gait, reduced premature mortality, improved social behaviour and memory function, and reduced anxiety-like and depressive-like behaviours. CONCLUSION AND IMPLICATIONS: We are the first to demonstrate a potential disease-modifying effect of cannabidiol in animal models of Dravet syndrome. Cannabidiol treatment reduced premature mortality and improved several behavioural co-morbidities in Dravet syndrome mice. These crucial findings may be translated into human therapy to address behavioural co-morbidities associated with Dravet syndrome.

Pawasarat, I. M., E. M. Schultz, et al. (2020). "The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain." J Palliat Med **23**(6): 809-816.

Background: The opioid epidemic has spurred investigations for nonopioid options, yet limited research persists on medical marijuana's (MMJ) efficacy in managing cancer-related symptoms. Objective: We sought to characterize MMJ's role on symptomatic relief and opioid consumption in the oncologic population. Design: Retrospective chart review of MMJ-certified oncology patients was performed. Divided patients into MMJ use [MMJ(+)] versus no use [MMJ(-)], and Edmonton Symptom Assessment System (ESAS)-reported pain cohorts: "mild-moderate" versus "severe." Measurements: Medical records were reviewed for ESAS, to measure physical and emotional symptoms, and opiate consumption, converted into morphine milligram equivalents (MME). Minimal clinically important differences were determined. Wilcoxon signed-rank tests determined statistical significance between MMJ-certification and most recent palliative care visit. Results: Identified 232 patients [95/232 MMJ(-); 137/232 MMJ(+)]. Pain, physical and total ESAS significantly improved for total MMJ(-) and MMJ(+); however, only MMJ(+) significantly improved emotional ESAS. MMJ(-) opioid consumption increased by 23% (97.5-120 mg/day MME, p = 0.004), while it remained constant (45-45 mg/day MME, p = 0.522) in MMJ(+). Physical and total ESAS improved in mild-moderate-MMJ(-) and MMJ(+). Pain and emotional symptoms worsened in MMJ(-); while MMJ(+)'s pain remained unchanged and emotional symptoms improved. MMJ(-) opioid consumption increased by 29% (90-126 mg/day MME, p = 0.012); while MMJ(+)'s decreased by 33% (45-30 mg/day MME, p = 0.935). Pain, physical, emotional, and total ESAS scores improved in severe-MMJ(-) and MMJ(+); opioid consumption reduced by 22% in MMJ(-) (135-106 mg/day MME, p = 0.124) and 33% in MMJ(+) (90-60 mg/day MME, p = 0.421). Conclusions: MMJ(+) improved oncology patients' ESAS scores despite opioid dose reductions and should be considered a viable adjuvant therapy for palliative management.

Pellati, F., V. Borgonetti, et al. (2018). "Cannabis sativa L. and Nonpsychoactive Cannabinoids: Their Chemistry and Role against Oxidative Stress, Inflammation, and Cancer." Biomed Res Int **2018**: 1691428.

In the last decades, a lot of attention has been paid to the compounds present in medicinal Cannabis sativa L., such as Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and cannabidiol (CBD), and their effects on inflammation and cancer-related pain. The National Cancer Institute (NCI) currently recognizes medicinal C. sativa as an effective treatment for providing relief in a number of symptoms associated with cancer, including pain, loss of appetite, nausea and vomiting, and anxiety. Several studies have described CBD as a multitarget molecule, acting as an adaptogen, and as a modulator, in different ways, depending on the type and location of disequilibrium both in the brain and in the body, mainly interacting with specific receptor proteins CB1 and CB2. CBD is present in both medicinal and fibre-type C. sativa plants, but, unlike Delta(9)-THC, it is completely nonpsychoactive. Fibre-type C. sativa (hemp) differs from medicinal C. sativa, since it contains only few levels of Delta(9)-THC and high levels of CBD and related nonpsychoactive compounds. In recent years, a number of preclinical researches have been focused on the role of CBD as an anticancer molecule, suggesting CBD (and CBD-like molecules present in the hemp extract) as a possible candidate for future clinical trials. CBD has been found to possess antioxidant activity in many studies, thus suggesting a possible role in the prevention of both neurodegenerative and cardiovascular diseases. In animal models, CBD has been shown to inhibit the progression of several cancer types. Moreover, it has been found that coadministration of CBD and Delta(9)-THC, followed by radiation therapy, causes an increase of autophagy and apoptosis in cancer cells. In addition, CBD is able to inhibit cell proliferation and to increase apoptosis in different types of cancer models. These activities seem to involve also alternative pathways, such as the interactions with TRPV and GRP55 receptor complexes. Moreover, the finding that the acidic precursor of CBD (cannabidiolic acid, CBDA) is able to inhibit the migration of breast cancer cells and to downregulate the proto-oncogene c-fos and the cyclooxygenase-2 (COX-2) highlights the possibility that CBDA might act on a common pathway of inflammation and cancer mechanisms, which might be responsible for its anticancer activity. In the light of all these findings, in this review we explore the effects and the molecular mechanisms of CBD on inflammation and cancer processes, highlighting also the role of minor cannabinoids and noncannabinoids constituents of Delta(9)-THC deprived hemp.

Penn, A. (2019). "Cannabinoids and Mental Health, Part 1: The Endocannabinoid System and Exogenous Cannabinoids." J Psychosoc Nurs Ment Health Serv 57(9): 7-10.

The increasing public acceptance of cannabis and the proliferation of cannabis products in the marketplace has coincided with more patients using the drug as a substitute for psychiatric medications or as an adjunctive treatment modality for psychiatric conditions, despite limited evidence of efficacy. With a goal of furthering harm-reduction efforts in psychiatric nursing, the current article reviews the fundamentals of the endocannabinoid system in humans and the exogenous phytocannabinoids that act on this regulatory neurotransmitter system. The basics of cannabis botany are also reviewed to help nurse clinicians understand the heterogeneous nature of cannabis products. This foundational knowledge will help improve clinical interactions with patients who use cannabis and provide the necessary understanding of cannabinoids needed to undertake further scientific query into their purported benefits in psychiatric disease states. [Journal of Psychosocial Nursing and Mental Health Services, 57(9), 7-10.].

Penner, I.-K. and H.-P. Hartung (2019). "The dark side of the moon: looking beyond beneficial effects of cannabis use in multiple sclerosis." Brain 142(9): 2552-2555.

This scientific commentary refers to ‘Coming off cannabis: a cognitive and magnetic resonance imaging study in patients with multiple sclerosis’, by Feinstein et al. (doi:10.1093/brain/awz213).Individuals with multiple sclerosis suffer from a variety of symptoms reflecting impairment of visual, motor and somatosensory pathways as well as cognitive domains that are insufficiently targeted by the commonly used immunotherapies. Evidence-based symptomatic treatment approaches are therefore urgently needed. Because of the absence of high quality symptomatic treatment studies with medical cannabis (distinct from purified cannabis extracts), some patients with multiple sclerosis use cannabis for self-management of their symptoms despite their awareness of legal issues (Gustavsen et al., 2019). Legal issues are, however, likely to become less relevant in the future as increasing numbers of countries legalize cannabis for medical and recreational use, including Canada, Uruguay, some states of the USA, South Africa, and Georgia, or for medical use alone, e.g. Thailand and Great Britain. Many central European countries are also planning to approve marijuana for medical (and in some cases recreational use) as well. Thus, it may be assumed that the use of medical cannabis by patients with multiple sclerosis will increase substantially in the next few years. Evidence for a beneficial effect of cannabis use in patients with multiple sclerosis has so far been limited to patient-reported improvements in spasticity, central pain, and bladder symptoms, but these studies were unable to verify the improvements with objective measures (Whiting et al., 2015). Cognitive impairment is another key symptom in multiple sclerosis, affecting 40–80% of patients often early in the disease course, and with marked impact on quality of life and working ability (Kobelt et al., 2017). A decline in cognitive function is a daunting prospect for many patients with multiple sclerosis, and a situation from which some may be tempted to escape by means of cannabis consumption. However, evidence from cross-sectional studies comparing patients who are currently using versus not using cannabis does not speak in favour of this strategy. Instead, negative effects of cannabis consumption have been demonstrated on information processing speed, working memory and executive functions, all cognitive domains that are highly relevant in daily life (Honarmand et al., 2011). Conversely, data from a 48-week, placebo-controlled study of the cannabis extract, nabiximols, in patients with multiple sclerosis experiencing spasticity revealed no adverse effects on cognition as measured by the Paced Auditory Serial Addition Test (PASAT) (Vachova et al., 2014). In this issue of Brain, Feinstein and co-workers examine not only the effects of cannabis use on cognition, but also investigate whether effects on cognitive performance may be reversed when patients with multiple sclerosis stop using cannabis (Feinstein et al., 2019).

Peres, F. F., A. C. Lima, et al. (2018). "Cannabidiol as a Promising Strategy to Treat and Prevent Movement Disorders?" Frontiers in Pharmacology **9**: 482.

Movement disorders such as Parkinson’s disease and dyskinesia are highly debilitating conditions linked to oxidative stress and neurodegeneration. When available, the pharmacological therapies for these disorders are still mainly symptomatic, do not benefit all patients and induce severe side effects. Cannabidiol is a non-psychotomimetic compound from Cannabis sativa that presents antipsychotic, anxiolytic, anti-inflammatory, and neuroprotective effects. Although the studies that investigate the effects of this compound on movement disorders are surprisingly few, cannabidiol emerges as a promising compound to treat and/or prevent them. Here, we review these clinical and pre-clinical studies and draw attention to the potential of cannabidiol in this field.

Peres, F. F., V. Almeida, et al. (2017). Chapter 81 - Cannabidiol: An Overview of its Antipsychotic Properties A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 787-794.

Abstract Schizophrenia presents positive, negative, and cognitive symptoms. The available antipsychotic drugs treat mainly the positive symptoms, having a low therapeutic efficacy against the negative and cognitive symptoms. Furthermore, they induce important motor and metabolic side effects. Therefore, the search for new therapeutic strategies is crucial. Alterations in the endocannabinoid system seem to be implicated in the pathophysiology of schizophrenia. In this scenario, cannabidiol (CBD)—a nonpsychotomimetic compound of cannabis—emerges as a potential new therapeutic strategy for schizophrenia. This chapter reviews the available data regarding the antipsychotic effects of CBD. CBD seems able to treat the positive symptoms of schizophrenia, and represents an advance with regard to the existing antipsychotics, since it might also be effective against the negative and cognitive symptoms. Moreover, significant side effects are not seen with cannabidiol treatment. However, despite the auspicious evidence, further clinical and preclinical studies are still necessary to strengthen CBD’s antipsychotic profile.

Pereira, L., M. J. Núñez-Iglesias, et al. (2020). "Nursing Students' Knowledge and Attitudes Regarding Medical Marijuana: A Descriptive Cross-Sectional Study." International journal of environmental research and public health **17**(7): 2492.

Marijuana use for medical purposes dates back to ancient times. Despite its high therapeutic potential, its adverse effects have raised important legal restrictions. However, this situation in Spain may soon undergo significant changes, without anyone so far having studied the knowledge and/or the level of acceptance of medical marijuana by future healthcare professionals. The aim of the present study was to determine nursing students' knowledge of and attitudes towards medical marijuana. A cross-sectional design was used. A total of 578 nursing students from the University of Santiago de Compostela (Spain), ≥18 years old and of both sexes, were invited to complete the Spanish version of the questionnaire "Medical Marijuana" between January and May 2019. A total of 364 students decided to participate in the study. More than 75% of the students agreed with the legalization of medical marijuana, although their knowledge and confidence levels regarding efficacy, safety and drug interactions of medical marijuana were low. Nursing students showed a clear lack of knowledge about medical marijuana and thus, in light of possible regulatory changes, it would be necessary to strengthen the training of nurses with respect to medical marijuana in order to make responsible use of it.

Pergam, S. A., M. C. Woodfield, et al. (2017). "Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use." Cancer **123**(22): 4488-4497.

BACKGROUND: Cannabis is purported to alleviate symptoms related to cancer treatment, although the patterns of use among cancer patients are not well known. This study was designed to determine the prevalence and methods of use among cancer patients, the perceived benefits, and the sources of information in a state with legalized cannabis. METHODS: A cross-sectional, anonymous survey of adult cancer patients was performed at a National Cancer Institute-designated cancer center in Washington State. Random urine samples for tetrahydrocannabinol provided survey validation. RESULTS: Nine hundred twenty-six of 2737 eligible patients (34%) completed the survey, and the median age was 58 years (interquartile range [IQR], 46-66 years). Most had a strong interest in learning about cannabis during treatment (6 on a 1-10 scale; IQR, 3-10) and wanted information from cancer providers (677 of 911 [74%]). Previous use was common (607 of 926 [66%]); 24% (222 of 926) used cannabis in the last year, and 21% (192 of 926) used cannabis in the last month. Random urine samples found similar percentages of users who reported weekly use (27 of 193 [14%] vs 164 of 926 [18%]). Active users inhaled (153 of 220 [70%]) or consumed edibles (154 of 220 [70%]); 89 (40%) used both modalities. Cannabis was used primarily for physical (165 of 219 [75%]) and neuropsychiatric symptoms (139 of 219 [63%]). Legalization significantly increased the likelihood of use in more than half of the respondents. CONCLUSIONS: This study of cancer patients in a state with legalized cannabis found high rates of active use across broad subgroups, and legalization was reported to be important in patients' decision to use. Cancer patients desire but are not receiving information about cannabis use during their treatment from oncology providers. Cancer 2017;123:4488-97. (c) 2017 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Perucca, E. (2017). "Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?" Journal of epilepsy research 7(2): 61-76.

The interest in cannabis-based products for the treatment of refractory epilepsy has skyrocketed in recent years. Marijuana and other cannabis products with high content in Δ(9) - tetrahydrocannabinol (THC), utilized primarily for recreational purposes, are generally unsuitable for this indication, primarily because THC is associated with many undesired effects. Compared with THC, cannabidiol (CBD) shows a better defined anticonvulsant profile in animal models and is largely devoid of adverse psychoactive effects and abuse liability. Over the years, this has led to an increasing use of CBD-enriched extracts in seizure disorders, particularly in children. Although improvement in seizure control and other benefits on sleep and behavior have been often reported, interpretation of the data is made difficult by the uncontrolled nature of these observations. Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last 12 months, with the completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes. Based on currently available information, however, it is unclear whether the improved seizure control described in these trials was related to a direct action of CBD, or was mediated by drug interactions with concomitant medications, particularly a marked increased in plasma levels of N-desmethylclobazam, the active metabolite of clobazam. Clarification of the relative contribution of CBD to improved seizure outcome requires re-assessment of trial data for the subgroup of patients not comedicated with clobazam, or the conduction of further studies controlling for the confounding effect of this interaction.

Petker, T., M. M. Owens, et al. (2019). "Cannabis involvement and neuropsychological performance: findings from the Human Connectome Project." J Psychiatry Neurosci 44(6): 414-422.

Background: There is evidence that heavy cannabis use is associated with decrements in cognitive performance, but findings are mixed and studies are often limited by small sample sizes and narrow adjustment for potential confounding variables. In a comparatively large sample, the current study examined associations between multiple indicators of cannabis use in relation to performance on a variety of neuropsychological tasks. Methods: Participants were 1121 adults (54% female) enrolled in the Human Connectome Project. Cannabis involvement comprised recent cannabis use (positive tetrahydrocannabinol screen), total number of lifetime uses, cannabis use disorder and age at first use. The neuropsychological battery comprised performance in episodic memory, fluid intelligence, attention, working memory, executive function, impulsive decision-making, processing speed and psychomotor dexterity. Covariates were age, sex, income, family structure and alcohol and tobacco use. Results: Positive urinary tetrahydrocannabinol status was associated with worse performance in episodic memory and processing speed, and positive cannabis use disorder status was associated with lower fluid intelligence (all p < 0.005). No other significant associations were present. Limitations: The sample was limited to young adults aged 22-36 years. The measures of cannabis involvement were relatively coarse. Conclusion: Beyond an array of potential confounders, recent cannabis use was associated with deficits in memory and psychomotor performance, and cannabis use disorder was associated with lower overall cognitive functioning in a large normative sample of adults. The findings pertaining to recent use have particular relevance for occupational settings.

Philpot, L., J. Ebbert, et al. (2019). "A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers." BMC Family Practice **20**.

Background Healthcare providers play a critical role in facilitating patient access to medical cannabis. However, previous surveys suggest only a minority of providers believe that medical cannabis confers benefits to patients. Significant new knowledge about the potential benefits and harms of medical cannabis has recently emerged. Understanding current attitudes and beliefs of providers may provide insight into the ongoing challenges they face as states expand access to medical cannabis. Methods We conducted an electronic survey of primary care providers in a large Minnesota-based healthcare system between January 23 and February 5, 2018. We obtained information about provider characteristics, attitudes and beliefs about medical cannabis, provider comfort level in answering patient questions about medical cannabis, and whether providers were interested in receiving additional education. Results Sixty-two providers completed the survey (response rate 31%; 62/199). Seventy-six percent of respondents were physicians and the average age was 46.3 years. A majority of providers believed (“strongly agree” or “somewhat agree”) that medical cannabis was a legitimate medical therapy (58.1%) and 38.7% believed that providers should be offering to patients for managing medical conditions. A majority (> 50%) of providers believed that medical cannabis was helpful for treating the qualifying medical conditions of cancer, terminal illness, and intractable pain. A majority of providers did not know if medical cannabis was effective for managing nearly one-half of the other state designated qualifying medical conditions. Few believed that medical cannabis improved quality of life domains. Over one-third of providers believed that medical cannabis interacted with medical therapies. One-half of providers were not ready to or did not want to answer patient questions about medical cannabis, and the majority of providers wanted to learn more about it. Conclusions Healthcare providers generally believe that medical cannabis is a legitimate medical therapy. Provider knowledge gaps about the effectiveness of medical cannabis for state designated qualifying conditions need to be addressed, and accurate information about the potential for drug interactions needs to be disseminated to address provider concerns. Clinical trial data about how medical cannabis improves patient quality of life domains is desperately needed as this information can impact clinical decision-making. Electronic supplementary material The online version of this article (10.1186/s12875-019-0906-y) contains supplementary material, which is available to authorized users.

Picardo, S., G. G. Kaplan, et al. (2019). "Insights into the role of cannabis in the management of inflammatory bowel disease." Therap Adv Gastroenterol 12: 1756284819870977.

Over the last decade, interest in the therapeutic potential of cannabis and its constituents (e.g. cannabidiol) in the management of inflammatory bowel diseases (IBD) has escalated. Cannabis has been increasingly approved for a variety of medical conditions in several jurisdictions around the world. In animal models, cannabinoids have been shown to improve intestinal inflammation in experimental models of IBD through their interaction with the endocannabinoid system. However, the few randomized controlled trials of cannabis or cannabidiol in patients with IBD have not demonstrated efficacy in modulating inflammatory disease activity. Cannabis may be effective in the symptomatic management of IBD. Given the increasing utilization and cultural acceptance of cannabis, physicians need to be aware of its safety and efficacy in order to better counsel patients. The aim of this review is to provide an overview of the role of cannabis in the management of patients with IBD.

Pierre Flor-Henry, Y. S. (2018). "Brain Changes during Cannabis-Induced Psychosis: Clarifying the Marijuana Medicine/Harm Dichotomy." Journal of Psychiatry and Brain Science **3**(5).

Marijuana is the most widely consumed recreational drug in the world. In Canada, physicians are experiencing increasing pressure to prescribe medical marijuana, with proposed legalization coming in late 2018. The use of marijuana in the psychiatric population is increasing, and the prescribing process is largely unregulated. In spite of several medicinal indications, chronic marijuana use is associated with serious consequences including early-onset psychosis, addiction, persistent psychosocial dysfunction, and neuropsychological abnormalities.

In this paper, we present the first spectral electroencephalography (EEG) study of brain changes during cannabis-induced psychosis coupled with a comprehensive review of the literature on medicinal and recreational marijuana use. The findings suggest that psychotic symptoms following cannabis are distinct from schizophrenic and affective psychoses, and occur as the consequence of a generalized shift to right hemispheric dominance. This is coupled with abnormal activation sources in the excitatory beta and gamma bands in the left temporo-parietal region, with impaired engagement of the relevant networks in both cognitive and spatial goal-directed tasks. Detailed recommendations for public education and prescribing process of medicinal marijuana use are discussed.

Pizzol, D., J. Demurtas, et al. (2019). "Relationship Between Cannabis Use and Erectile Dysfunction: A Systematic Review and Meta-Analysis." American Journal of Men's Health 13(6): 1557988319892464.

Globally, there is increasing usage and legalization of cannabis. In addition to its reported therapeutic effects, cannabis has several health risks which are not clearly defined. Erectile dysfunction (ED) is the most common male sexual disorder and there are plausible mechanisms linking cannabis use to ED. No attempt has been made to collate the literature on this topic. The aim of this review was to summarize the prevalence and risk of ED in cannabis users compared to controls.A systematic review of major databases from inception to January 1, 2019, without language restriction, was undertaken to identify studies investigating cannabis use and presence of ED. The analysis compared the prevalence of ED in cannabis users versus controls. Consequently, the odds ratio (OR) with 95% confidence intervals (CI) was calculated, applying a random-effect model.Five case?control studies were included with data from 3,395 healthy men, 1,035 using cannabis (smoking) and 2,360 nonusers. The overall prevalence of ED in cannabis users was 69.1% (95% CI: 38.0?89.1), whilst the correspondent figure in controls was 34.7% (95% CI: 20.3?52.7). The OR of ED in cannabis users was almost four times that of controls (OR = 3.83; 95% CI: 1.30?11.28; p = .02), even if characterized by high heterogeneity (I2 = 90%) and the prediction intervals overlapped 1.00 (95% CI: 0.35?7.26).Data suggest that ED is twice as high in cannabis users compared to controls. Future longitudinal research is needed to confirm/refute this and explore if a dose?response relationship between cannabis and ED may be evident.

Poli, P., F. Crestani, et al. (2018). "Medical Cannabis in Patients with Chronic Pain: Effect on Pain Relief, Pain Disability, and Psychological aspects. A Prospective Non randomized Single Arm Clinical Trial." Clin Ter 169(3): e102-e107.

BACKGROUND: There is an increasing interest in the medical use of cannabis, particularly in the treatment of chronic pain. OBJECTIVES: The aim is to evaluate the effects of cannabis use and the associated benefits reported by patients with various chronic pain diagnoses. MATERIAL AND METHODS: A total of 338 patients with different chro- nic pain conditions were treated with a Cannabis Flos 19% decoction for 12 months, in addition to their pharmacological therapy. Baseline levels for pain medications, pain intensity, pain disability, anxiety and depression were recorded at 1, 3, 6 and 12 months. RESULTS: Pain intensity records a statistically significant reduction from Baseline to 12 months follow up (X(2) 61.375; P<0,001); the im- provements from Baseline to 12 months follow up are also recorded in pain disability (X(2) 39.423; P<0,001) and in anxiety and depression symptoms (X(2)30.362; P<0,001; X(2)27.786; P<0,001). CONCLUSIONS: Our study suggest that Cannabis therapy, as an adjun- ct a traditional analgesic therapy, can be an efficacious tool to make more effective the management of chronic pain and its consequences on functional and psychological dimension. Further randomized, controlled trials are needed to confirm our conclusions.

Powell, D., R. L. Pacula, et al. (2018). "Do medical marijuana laws reduce addictions and deaths related to pain killers?" J Health Econ **58**: 29-42.

Recent work finds that medical marijuana laws reduce the daily doses filled for opioid analgesics among Medicare Part-D and Medicaid enrollees, as well as population-wide opioid overdose deaths. We replicate the result for opioid overdose deaths and explore the potential mechanism. The key feature of a medical marijuana law that facilitates a reduction in overdose death rates is a relatively liberal allowance for dispensaries. As states have become more stringent in their regulation of dispensaries, the protective value generally has fallen. These findings suggest that broader access to medical marijuana facilitates substitution of marijuana for powerful and addictive opioids.

Pratt, M., A. Stevens, et al. (2019). "Benefits and harms of medical cannabis: a scoping review of systematic reviews." Systematic Reviews 8(1): 320.

There has been increased interest in the role of cannabis for treating medical conditions. The availability of different cannabis-based products can make the side effects of exposure unpredictable. We sought to conduct a scoping review of systematic reviews assessing benefits and harms of cannabis-based medicines for any condition.

Pretzsch, C. M., B. Voinescu, et al. (2019). "The effect of cannabidiol (CBD) on low-frequency activity and functional connectivity in the brain of adults with and without autism spectrum disorder (ASD)." J Psychopharmacol: 269881119858306.

BACKGROUND: The potential benefits of cannabis and its major non-intoxicating component cannabidiol (CBD) are attracting attention, including as a potential treatment in neurodevelopmental disorders such as autism spectrum disorder (ASD). However, the neural action of CBD, and its relevance to ASD, remains unclear. We and others have previously shown that response to drug challenge can be measured using functional magnetic resonance imaging (fMRI), but that pharmacological responsivity is atypical in ASD. AIMS: We hypothesized that there would be a (different) fMRI response to CBD in ASD.

METHODS: To test this, task-free fMRI was acquired in 34 healthy men (half with ASD) following oral administration of 600 mg CBD or matched placebo (random order; double-blind administration). The 'fractional amplitude of low-frequency fluctuations' (fALFF) was measured across the whole brain, and, where CBD significantly altered fALFF, we tested if functional connectivity (FC) of those regions was also affected by CBD.

RESULTS: CBD significantly increased fALFF in the cerebellar vermis and the right fusiform gyrus. However, post-hoc within-group analyses revealed that this effect was primarily driven by the ASD group, with no significant change in controls. Within the ASD group only, CBD also significantly altered vermal FC with several of its subcortical (striatal) and cortical targets, but did not affect fusiform FC with other regions in either group.

CONCLUSION: Our results suggest that, especially in ASD, CBD alters regional fALFF and FC in/between regions consistently implicated in ASD. Future studies should examine if this affects the complex behaviours these regions modulate.

Pritchard, E. R., L. Dayer, et al. (2019). "Effect of cannabis on opioid use in patients with cancer receiving palliative care." Journal of the American Pharmacists Association.

Objective Opioids are the primary therapy for cancer-related pain in patients receiving palliative care. More states are legalizing medical cannabis, which may provide a pain management alternative for some of these patients. This study aimed to estimate the effect of cannabis on opioid use in patients with cancer receiving palliative care. Methods This was a retrospective cohort study of patients with cancer at an academic medical center palliative care clinic. The primary outcome was change in morphine equivalent daily dose (MEDD) from baseline to 84-day follow-up in the cannabis plus opioid group compared to that in the opioid-only group. Results A total of 83 patients were included: 61 in the opioid monotherapy group and 22 in the cannabis plus opioid group. An increase in MEDD from the baseline to 84 days was seen in both the opioid monotherapy and opioid plus cannabis group (28.8 vs. 10.8); however, the study lacked power to detect a statistical difference. Conclusion A possibly meaningful difference in MEDD increase was seen when comparing the opioid monotherapy group with the opioid plus cannabis group. However, the study was not powered to test this hypothesis; the findings suggest that further research is warranted to determine the impact of cannabis use on opioid dosing in patients receiving palliative care for cancer.

Purcell, C., A. Davis, et al. (2019). "Reduction of Benzodiazepine Use in Patients Prescribed Medical Cannabis." Cannabis and Cannabinoid Research 4(3): 214-218.

Abstract Background: Benzodiazepines are a class of medication with sedative properties, commonly used for anxiety and other neurological conditions. These medications are associated with several well-known adverse effects. This observational study aims to investigate the reduction of benzodiazepine use in patients using prescribed medical cannabis. Methods: A retrospective analysis was performed on a cohort of 146 medical cannabis patients (average age 47 years, 61% female, 54% reporting prior use of cannabis) who reported benzodiazepine use at initiation of cannabis therapy. These data are a part of a database gathered by a medical cannabis clinic (Canabo Medical). Descriptive statistics were used to quantify associations of the proportion of benzodiazepine use with time on medical cannabis therapy. Results: After completing an average 2-month prescription course of medical cannabis, 30.1% of patients had discontinued benzodiazepines. At a follow-up after two prescriptions, 65 total patients (44.5%) had discontinued benzodiazepines. At the final follow-up period after three medical cannabis prescription courses, 66 total patients (45.2%) had discontinued benzodiazepine use, showing a stable cessation rate over an average of 6 months. Conclusion: Within a cohort of 146 patients initiated on medical cannabis therapy, 45.2% patients successfully discontinued their pre-existing benzodiazepine therapy. This observation merits further investigation into the risks and benefits of the therapeutic use of medical cannabis and its role relating to benzodiazepine use.

Background: Benzodiazepines are a class of medication with sedative properties, commonly used for anxiety and other neurological conditions. These medications are associated with several well-known adverse effects. This observational study aims to investigate the reduction of benzodiazepine use in patients using prescribed medical cannabis. Methods: A retrospective analysis was performed on a cohort of 146 medical cannabis patients (average age 47 years, 61% female, 54% reporting prior use of cannabis) who reported benzodiazepine use at initiation of cannabis therapy. These data are a part of a database gathered by a medical cannabis clinic (Canabo Medical). Descriptive statistics were used to quantify associations of the proportion of benzodiazepine use with time on medical cannabis therapy. Results: After completing an average 2-month prescription course of medical cannabis, 30.1% of patients had discontinued benzodiazepines. At a follow-up after two prescriptions, 65 total patients (44.5%) had discontinued benzodiazepines. At the final follow-up period after three medical cannabis prescription courses, 66 total patients (45.2%) had discontinued benzodiazepine use, showing a stable cessation rate over an average of 6 months. Conclusion: Within a cohort of 146 patients initiated on medical cannabis therapy, 45.2% patients successfully discontinued their pre-existing benzodiazepine therapy. This observation merits further investigation into the risks and benefits of the therapeutic use of medical cannabis and its role relating to benzodiazepine use.

Ramer, R. and B. Hinz (2017). Chapter Twelve - Cannabinoids as Anticancer Drugs. Advances in Pharmacology. D. Kendall and S. P. H. Alexander, Academic Press. **80:** 397-436.

The endocannabinoid system encompassing cannabinoid receptors, endogenous receptor ligands (endocannabinoids), as well as enzymes conferring the synthesis and degradation of endocannabinoids has emerged as a considerable target for pharmacotherapeutical approaches of numerous diseases. Besides palliative effects of cannabinoids used in cancer treatment, phytocannabinoids, synthetic agonists, as well as substances that increase endogenous endocannabinoid levels have gained interest as potential agents for systemic cancer treatment. Accordingly, cannabinoid compounds have been reported to inhibit tumor growth and spreading in numerous rodent models. The underlying mechanisms include induction of apoptosis, autophagy, and cell cycle arrest in tumor cells as well as inhibition of tumor cell invasion and angiogenic features of endothelial cells. In addition, cannabinoids have been shown to suppress epithelial-to-mesenchymal transition, to enhance tumor immune surveillance, and to support chemotherapeutics’ effects on drug-resistant cancer cells. However, unwanted side effects include psychoactivity and possibly pathogenic effects on liver health. Other cannabinoids such as the nonpsychoactive cannabidiol exert a comparatively good safety profile while exhibiting considerable anticancer properties. So far experience with anticarcinogenic effects of cannabinoids is confined to in vitro studies and animal models. Although a bench-to-bedside conversion remains to be established, the current knowledge suggests cannabinoid compounds to serve as a group of drugs that may offer significant advantages for patients suffering from cancer diseases. The present review summarizes the role of the endocannabinoid system and cannabinoid compounds in tumor progression.

Ramar, K., I. M. Rosen, et al. (2018). "Medical Cannabis and the Treatment of Obstructive Sleep Apnea: An American Academy of Sleep Medicine Position Statement." J Clin Sleep Med 14(4): 679- 681.

ABSTRACT: The diagnosis and effective treatment of obstructive sleep apnea (OSA) in adults is an urgent health priority. Positive airway pressure (PAP) therapy remains the most effective treatment for OSA, although other treatment options continue to be explored. Limited evidence citing small pilot or proof of concept studies suggest that the synthetic medical cannabis extract dronabinol may improve respiratory stability and provide benefit to treat OSA. However, side effects such as somnolence related to treatment were reported in most patients, and the long-term effects on other sleep quality measures, tolerability, and safety are still unknown. Dronabinol is not approved by the United States Food and Drug Administration (FDA) for treatment of OSA, and medical cannabis and synthetic extracts other than dronabinol have not been studied in patients with OSA. The composition of cannabinoids within medical cannabis varies significantly and is not regulated. Synthetic medical cannabis may have differential effects, with variable efficacy and side effects in the treatment of OSA. Therefore, it is the position of the American Academy of Sleep Medicine (AASM) that medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA due to unreliable delivery methods and insufficient evidence of effectiveness, tolerability, and safety. OSA should be excluded from the list of chronic medical conditions for state medical cannabis programs, and patients with OSA should discuss their treatment options with a licensed medical provider at an accredited sleep facility. Further research is needed to understand the functionality of medical cannabis extracts before recommending them as a treatment for OSA.

Rein, J. L. (2020). "The nephrologist's guide to cannabis and cannabinoids." Curr Opin Nephrol Hypertens **29**(2): 248-257.

PURPOSE OF REVIEW: Cannabis (marijuana, weed, pot, ganja, Mary Jane) is the most commonly used federally illicit drug in the United States. The present review provides an overview of cannabis and cannabinoids with relevance to the practice of nephrology so that clinicians can best take care of patients. RECENT FINDINGS: Cannabis may have medicinal benefits for treating symptoms of advanced chronic kidney disease (CKD) and end-stage renal disease including as a pain adjuvant potentially reducing the need for opioids. Cannabis does not seem to affect kidney function in healthy individuals. However, renal function should be closely monitored in those with CKD, the lowest effective dose should be used, and smoking should be avoided. Cannabis use may delay transplant candidate listing or contribute to ineligibility. Cannabidiol (CBD) has recently exploded in popularity. Although generally well tolerated, safe without significant side effects, and effective for a variety of neurological and psychiatric conditions, consumers have easy access to a wide range of unregulated CBD products, some with inaccurate labeling and false health claims. Importantly, CBD may raise tacrolimus levels. SUMMARY: Patients and healthcare professionals have little guidance or evidence regarding the impact of cannabis use on people with kidney disease. This knowledge gap will remain as long as federal regulations remain prohibitively restrictive towards prospective research.

Reithmeier, D., R. Tang-Wai, et al. (2018). "The protocol for the Cannabidiol in children with refractory epileptic encephalopathy (CARE-E) study: a phase 1 dosage escalation study." BMC Pediatr 18(1): 221.

BACKGROUND: Initial studies suggest pharmaceutical grade cannabidiol (CBD) can reduce the frequency of convulsive seizures and lead to improvements in quality of life in children Research update –September 2018 affected by epileptic encephalopathies. With limited access to pharmaceutical CBD, Cannabis extracts in oil are becoming increasingly available. Physicians show reluctance to recommend Cannabis extracts given the lack of high quality safety data especially regarding the potential for harm caused by other cannabinoids, such as Delta(9)-tetrahydrocannabinol (Delta(9)-THC). The primary aims of the study presented in this protocol are (i) To determine whether CBD enriched Cannabis extract is safe and well-tolerated for pediatric patients with refractory epilepsy, (ii) To monitor the effects of CBD-enriched Cannabis extract on the frequency and duration of seizure types and on quality of life. METHODS: Twenty-eight children with treatment resistant epileptic encephalopathy ranging in age from 1 to 10 years will be recruited in four Canadian cities into an open-label, dose-escalation phase 1 trial. The primary objectives for the study are (i) To determine if the CBD-enriched Cannabis herbal extract is safe and well-tolerated for pediatric patients with treatment resistant epileptic encephalopathy and (ii) To determine the effect of CBD-enriched Cannabis herbal extract on the frequency and duration of seizures. Secondary objectives include (i) To determine if CBD enriched Cannabis herbal extracts alter steady-state levels of co-administered anticonvulsant medications. (ii) To assess the relation between dose escalation and quality of life measures, (iii) To determine the relation between dose escalation and steady state trough levels of bioactive cannabinoids. (iv) To determine the relation between dose escalation and incidence of adverse effects. DISCUSSION: This paper describes the study design of a phase 1 trial of CBD-enriched Cannabis herbal extract in children with treatment resistant epileptic encephalopathy. This study will provide the first high quality analysis of safety of CBD-enriched Cannabis herbal extract in pediatric patients in relation to dosage and pharmacokinetics of the active cannabinoids. TRIAL REGISTRATION: http://clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Dec 16. Identifier NCT03024827, Cannabidiol in Children with Refractory Epileptic Encephalopathy: CARE-E; 2017 Jan 19 [cited 2017 Oct]; Available from: http://clinicaltrials.gov/ct2/show/NCT03024827.

Ribeiro, L. and P. W. Ind (2018). "Marijuana and the lung: hysteria or cause for concern?" Breathe

(Sheff) 14(3): 196-205.

Increasing cannabis use and legalisation highlights the paucity of data we have on the safety of cannabis smoking for respiratory health. Unfortunately, concurrent use of tobacco among marijuana smokers makes it difficult to untangle individual effect of marijuana smoking. Chronic cannabis only smoking has been shown in large cohort studies to reduce forced expiratory volume in 1 s/forced vital capacity via increasing forced vital capacity in chronic use contrary to the picture seen in tobacco smoking. The cause of this is unclear and there are various proposed mechanisms including respiratory muscle training secondary to method of inhalation and acute anti-inflammatory effect and bronchodilation of cannabis on the airways. While cannabis smoke has been shown to increase symptoms of chronic bronchitis, it has not been definitively shown to be associated with shortness of breath or irreversible airway changes. The evidence surrounding the development of lung cancer is less clear; however, preliminary evidence does not suggest association. Bullous lung disease associated with marijuana use has long been observed in clinical practice but published evidence is limited to a total of 57 published cases and only one cross-sectional study looking at radiological changes among chronic users which did not report any increase in macroscopic emphysema. More studies are required to elucidate these missing points to further guide risk stratification, clinical diagnosis and management. Key points: Cannabis smoking has increased and is likely to increase further with relaxation of legalisation and medicinal use of cannabinoids. Chronic marijuana smoking often produces symptoms similar to those of chronic tobacco smoking such as cough, sputum production, shortness of breath.   
Research update –September 2018 and wheeze.Cessation of marijuana smoking is associated with a reduction in respiratory symptoms and no increased risk of chronic bronchitis.Spirometry changes seen in chronic marijuana smokers appear to differ from those in chronic tobacco smokers. In chronic marijuana smokers there is an increase in FVC as opposed to a definite decrease in FEV1.Multiple case series have demonstrated peripheral bullae in marijuana smokers, but no observational studies have elucidated the risk. There is currently no clear association between cannabis smoking and lung cancer, although the research is currently limited. Educational aims: To update readers on legalisation of recreational and medicinal cannabis. To summarise the evidence base surrounding the respiratory effects of inhaled marijuana use. To provide clinicians with an understanding of the main differences between cannabis and tobacco to be able to apply this to patient education. To highlight common respiratory problems among cannabis users and the need for recreational drug history taking.

Rice, J. and M. Cameron (2018). "Cannabinoids for Treatment of MS Symptoms: State of the Evidence." Curr Neurol Neurosci Rep 18(8): 50.

PURPOSE OF REVIEW: Cannabis and cannabinoids have been used medically and recreationally for thousands of years and recently there has been a growing body of research in this area. With increased access now that medical marijuana is available in many jurisdictions, patients and providers want to know more about the evidence for benefits and risks of cannabinoid use. This paper provides an overview of the available cannabinoid based formulations, a summary of the highest quality evidence for the use of cannabinoids for treating spasticity and pain associated with multiple sclerosis (MS), and a discussion of possible dosing regimens based on information from these studies. RECENT FINDINGS: Two recent high-quality systematic reviews concluded that the only strong evidence for medical marijuana in neurological disorders was for reducing the symptoms of patient-reported spasticity and central pain in MS and that the only complementary and alternative medicine (CAM) intervention in MS with strong supportive evidence was cannabinoids. Based on this review, they concluded that nabiximols (Sativex oral spray), oral cannabis extract (OCE), and synthetic tetrahydrocannabinol (THC) are probably effective at reducing patient-reported symptoms of spasticity in people with MS, but OCE and synthetic THC were not found to be effective for reducing physician-administered measures of spasticity. In addition, nabiximols, OCE, and synthetic THC are probably effective at reducing MS-related pain. Cannabinoids were generally well-tolerated. However, cannabis use has been associated with an increased risk of psychosis and schizophrenia in at-risk individuals, there is growing evidence that cannabis can increase the risk for cardiovascular diseases, including myocardial infarction (MI), hypertension, heart failure, and stroke, and a recently recognized adverse effect of cannabis is cannabinoid hyperemesis syndrome. The medical use of cannabinoids remains controversial. While cannabinoids have been studied for a variety of neurologic disorders, there is strongest evidence to indicate benefits in treatment of spasticity and neuropathic pain in multiple sclerosis. Although the best dose for an individual remains uncertain, most participants in the studies discussed in this paper used between 20 and 40 mg of THC a day in divided doses. Adverse events in studies were generally more common in the groups using cannabinoid products but serious adverse events were rare and cannabis products were generally well-tolerated. Cannabis use does appear to be associated with increased risk of certain adverse events, including psychosis, cardiovascular diseases, and cannabinoid hyperemesis syndrome.

Rimkus, C. and R. A. Didion (2018). "390 - Developing a Policy for Use of Medicinal and Non Medicinal Marijuana in Stem Cell Transplant Patients." Biology of Blood and Marrow Transplantation **24**(3, Supplement): S325-S326.

Recent years have brought about a rapid change in the approach that many states take towards the utilization of medical and non-medical marijuana. It is currently being used in multiple formulations (i.e. oils, edibles, topical) to manage a wide range of symptoms. Despite the more widespread use of medical marijuana, there are many misconceptions from the patients, family members and medical providers about its use. Given that there are potential added risks associated with using cannabinoids in stem cell transplant (SCT) patients, our center decided to embark on a process to provide medically and legally sound advice to patients.

Romero-Sandoval, E. A., J. E. Fincham, et al. (2018). "Cannabis for Chronic Pain: Challenges and

Considerations." Pharmacotherapy 38(6): 651-662.

The National Academies of Sciences, Engineering, and Medicine has found substantial evidence that cannabis (plant) is effective for the treatment of chronic pain in adults, and moderate evidence that oromucosal cannabinoids (extracts, especially nabiximols) improve short-term sleep disturbances in chronic pain. The paradoxical superiority of the cannabis plant over cannabinoid molecules represents a challenge for the medical community and the established processes that define modern pharmacy. The expanding and variable legalization of cannabis in multiple states nationwide represents an additional challenge for patients and the medical community because recreational and medicinal cannabis are irresponsibly overlapped. Cannabis designed for recreational use (containing high levels of active ingredients) is increasingly available to patients with chronic pain who do not find relief with current pharmacologic entities, which exposes patients to potential harm. This article analyzes the available scientific evidence to address controversial questions that the current state of cannabis poses for health care professionals and chronic pain patients and sets the basis for a more open discussion about the role of cannabis in modern medicine for pain management. A critical discussion on these points, the legal status of cannabis, and considerations for health care providers is presented.

Rog, D. J., T. J. Nurmikko, et al. (2005). "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis." Neurology **65**(6): 812.

Background: Central pain in multiple sclerosis (MS) is common and often refractory to treatment. Methods: We conducted a single-center, 5-week (1-week run-in, 4-week treatment), randomized, double-blind, placebo-controlled, parallel-group trial in 66 patients with MS and central pain states (59 dysesthetic, seven painful spasms) of a whole-plant cannabis-based medicine (CBM), containing delta-9-tetrahydrocannabinol:cannabidiol (THC:CBD) delivered via an oromucosal spray, as adjunctive analgesic treatment. Each spray delivered 2.7 mg of THC and 2.5 of CBD, and patients could gradually self-titrate to a maximum of 48 sprays in 24 hours. Results: Sixty-four patients (97%) completed the trial, 34 received CBM. In week 4, the mean number of daily sprays taken of CBM (n = 32) was 9.6 (range 2 to 25, SD = 6.0) and of placebo (n = 31) was 19.1 (range 1 to 47, SD = 12.9). Pain and sleep disturbance were recorded daily on an 11-point numerical rating scale. CBM was superior to placebo in reducing the mean intensity of pain (CBM mean change −2.7, 95% CI: −3.4 to −2.0, placebo –1.4 95% CI: −2.0 to −0.8, comparison between groups, p = 0.005) and sleep disturbance (CBM mean change –2.5, 95% CI: −3.4 to −1.7, placebo –0.8, 95% CI: −1.5 to −0.1, comparison between groups, p = 0.003). CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness, dry mouth, and somnolence. Cognitive side effects were limited to long-term memory storage. Conclusions: Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated.

Round, J. M., C. Lee, et al. (2020). "Changes in patient health questionnaire (PHQ-9) scores in adults with medical authorization for cannabis." BMC public health **20**(1): 987-987.

BACKGROUND: Legal access to medical cannabis is increasing world-wide. Despite this, there is a lack of evidence surrounding its efficacy on mental health outcomes, particularly, on depression. This study assesses the effect of medical cannabis on Patient Health Questionnaire (PHQ-9) scores in adult patients between 2014 and 2019 in Ontario and Alberta, Canada. METHODS: An observational cohort study of medically authorized cannabis patients in Ontario and Alberta. Overall change in PHQ-9 scores from baseline to follow-up were evaluated (mean change) over a time period of up to 3.2 years. RESULTS: 37,338 patients from the cohort had an initial PHQ-9 score recorded with 5103 (13.7%) patients having follow-up PHQ-9 scores. The average age was 54 yrs. (SD 15.7), 46% male, 50% noted depression at baseline. The average PHQ-9 score at baseline was 10.5 (SD 6.9), following a median follow-up time of 196 days (IQR: 77-451) the average final PHQ-9 score was 10.3 (SD 6.8) with a mean change of - 0.20 (95% CI: - 0.26, - 0.14, p-value < 0.0001). Overall, 4855 (95.1%) had no clinically significant change in their PHQ-9 score following medical cannabis use while 172 (3.4%) reported improvement and 76 (1.5%) reported worsening of their depression symptoms. CONCLUSIONS: Although the majority showed no clinically important changes in PHQ-9 scores, a number of patients showed improvement or deteriorations in PHQ-9 scores. Future studies should focus on the parallel use of screening questionnaires to control for PHQ-9 sensitivity and to explore potential factors that may have attributed to the improvement in scores pre- and post- 3-6 month time period.

Rower, J., A. King, et al. (2020). "Dronabinol Prescribing and Exposure Among Children and Young Adults Diagnosed with Cancer." Journal of Adolescent and Young Adult Oncology.

Purpose: The therapeutic utility of Cannabis in cancer is a topic of intense interest. Dronabinol is synthetic Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of Cannabis sativa, and is approved for treating refractory chemotherapy-induced nausea and vomiting. Little is known about dronabinol prescribing in children and young adults, and no published concentration data are available. This study evaluated national level dronabinol use and assessed concentrations of THC and its primary metabolites in patients with cancer <27 years of age prescribed dronabinol. Methods: Observational review of records from the Pediatric Health Information System (PHIS) and a regional network of hospitals in the Intermountain West, including a tertiary care children's hospital, Primary Children's Hospital (PCH), for inpatients <27 years of age prescribed dronabinol. Prospective blood samples were collected from children with cancer at PCH. Results: Across PHIS institutions, overall dronabinol prescribing aligned with the pharmacy records for those with cancer (p < 0.0001), and of these, 10.4% received dronabinol as inpatients. Blood collected within 72 hours of dronabinol administration was available from 10 children with a median age of 12.5 (range 6-17) years. Quantifiable concentrations were found in 4 (13%), 6 (20%), and 1 (3%) samples assayed for THC, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (COOH-THC), and 11-hydroxy-Δ9-tetrahydrocannabinol (OH-THC), respectively. THC concentrations ranged between 0.100 and 0.128 ng/mL and were not associated with dose. Conclusion: Dronabinol prescribing appears exclusive to patients diagnosed with cancer, and its use has increased steadily in the past decade. In a small sample of children administered dronabinol, THC and metabolite concentrations were consistently low or undetectable.

Runner, R. P., A. N. Luu, et al. (2020). "Use of Tetrahydrocannabinol and Cannabidiol Products in the Perioperative Period Around Primary Unilateral Total Hip and Knee Arthroplasty." J Arthroplasty **35**(6s): S138-s143.

BACKGROUND: Given the opioid crisis in America, patients are trying alternative medications including tetrahydrocannabinol (THC) and other cannabidiol (CBD) containing products in the perioperative period, especially in states where these products are legal. This study sought to analyze usage rates of CBD/THC products in the perioperative period for primary unilateral total hip and knee arthroplasty (THA/TKA) patients and identify a possible association with post-operative opioid use. METHODS: A prospective cohort of primary unilateral THA/TKA patients were enrolled at a single institution. Patients who completed detailed pain journals were retrospectively surveyed for CBD/THC product usage. Pain medications were converted to morphine milligram equivalents (MME). RESULTS: Data from 195 of the 210 patients (92.9% response rate) following primary arthroplasty were analyzed. Overall, 16.4% of arthroplasty-22.6% (n = 19) of TKA and 11.7% (n = 13) of THA-patients used CBD/THC products in the perioperative period. There was a wide variety of usage patterns among those using CBD/THC products. In comparing CBD/THC users and non-users, there was no significant difference in the length of narcotic use, total morphine milligram equivalents taken, narcotic pills taken, average post-op pain scores, the percentage of patients requiring a refill of narcotics, or length of stay. CONCLUSION: Understanding that CBD/THC usage was not consistent for patients who used these products, 22.6% of TKA and 11.7% of THA patients tried CBD/THC products in the perioperative period. In this small sample, CBD/THC use was not associated with a major effect on narcotic requirements. Further studies on the effects of CBD/THC are needed as these therapies become more widely available.

Ruzic Zecevic, D., M. Folic, et al. (2018). "Investigational cannabinoids in seizure disorders, what have

we learned thus far?" Expert Opin Investig Drugs **27**(6): 535-541.

INTRODUCTION: The anticonvulsant activity of cannabinoids attracted much attention in the last decade. Cannabinoids that are currently investigated with the intention of making them drugs for the treatment of epilepsy are cannabidiol, cannabidivarin, Delta9- tetrahydrocannabivarin, and Delta9-tetrahydrocannabinolic acid. Areas covered:In this review, the authors look at the results of preclinical and clinical studies with investigational cannabinoids. Relevant literature was searched for in MEDLINE, SCOPUS, EBSCO, GOOGLE SCHOLAR, and SCINDEX databases. Expert opinion: Preclinical studies confirmed anticonvulsant activity of cannabidiol and cannabidivarin in a variety of epilepsy models. While the results of clinical trials with cannabidivarin are still awaited, cannabidiol showed clear therapeutic benefit and good safety in patients with therapy-resistant seizures associated with Dravet syndrome and in patients with Lennox-Gastaut syndrome who have drop seizures. However, the full therapeutic potential of cannabinoids in treatment-resistant epilepsy needs to be investigated in the near future.

Ryan, J. E., S. C. Smeltzer, et al. (2020). "Parents’ experiences using medical cannabis for their child." Nursing Outlook **68**(3): 337-344.

Background Parents across the United States use medical cannabis for their children, often without professional guidance. These parents have become more expert on medical cannabis than most health professionals. Purpose Using a case-study design, this study was conducted to describe the experience of parents using medical cannabis for relief of seizures in their child or dependent. Methods Data were subjected to qualitative content analysis for the identification of patterns and themes. Findings Analysis of all data revealed seven themes including “Discovery of Cannabis as a Medication,” “Guidance on Dosing,” “Costs and Benefits of Cannabis,” “Distrust of the Pharmaceutical Industry,” “Federal Interference,” “God and Cannabis,” and “Changing Societal Perceptions about Medical Cannabis.” Discussion Themes revealed a complex, multifaceted experience. Many parents report benefit from medical cannabis, and are not hindered by the financial costs or uncertainties. Political and social influences have significant impact on the stigmatization and normalization of cannabis.

Rychert, M., C. Wilkins, et al. (2020). "Exploring medicinal use of cannabis in a time of policy change in New Zealand." N Z Med J **133**(1515): 54-69.

AIMS: To explore patterns of medicinal cannabis use prior to implementation of the new Medicinal Cannabis Scheme (MCS) in New Zealand. METHODS: An anonymous online convenience survey of 3,634 last-year medicinal users of cannabis promoted via Facebook™ from May to August 2019. RESULTS: Fifty percent of the sample were female, 18% were Māori and the median age was 38 years. The medical conditions for which cannabis was most often used were pain (81%), sleep (66%) and mental health conditions (64%). Respondents perceived cannabis to be an effective therapy and reported reducing use of other pharmaceutical medicines. Fifty-two percent reported side effects from cannabis use, including increased appetite (29%), drowsiness (12%), eye irritation (11%), dependency (10%), memory impairment (10%) and lack of energy (9%). Smoking was the dominant route of administration. Nearly half (47%) had discussed their use of cannabis with a medical professional in the previous year, while 14% had requested a prescription and 5% accessed a prescribed cannabis-based product (mostly oral CBD). CONCLUSION: Respondents self-medicated with cannabis to treat a wide range of health complaints. Only half discussed medicinal cannabis use with their medical professional, and a minority requested a prescription and used a prescribed cannabis-based product.

Saadeh, C. E. and D. R. Rustem (2018). "Medical Marijuana Use in a Community Cancer Center." Journal of Oncology Practice **14**(9): e566-e578.

Purpose: The primary purpose of this study was to compare the incidence of marijuana use between patients with early- versus advanced-stage cancers. Differences in adverse effects, drug-drug interactions, and drug-disease interactions between those who use marijuana and those who do not were also compared. Methods: Patients age 18 years and older who were receiving chemotherapy were asked to complete an electronic self-reported questionnaire. In addition to questions about patient demographics, current adverse effects, cancer type and stage, comorbidities, performance status, treatment regimen, and general marijuana use, those patients who used marijuana within the last 30 days (current marijuana users) were asked additional questions about the route and frequency of marijuana administration, about reason(s) for use, about possession of a marijuana card, and if they had received any counseling about marijuana. Drug-drug and drug-disease interactions were also analyzed. Results: The overall incidence of marijuana use was 18.3% (32 of 175 patients). The incidence of marijuana use in patients with early- versus advanced-stage cancers was 19.6% (11 of 56 patients) versus 17.6% (21 of 119 patients; P = .75). Patients who use marijuana reported more pain, nausea, appetite issues, and anxiety. There were more drug-drug interactions associated with marijuana use, primarily with concurrent CNS depressants. The frequency of drug-disease interactions between those who use marijuana versus those who do not was similar. Conclusion: Approximately one in five patients with cancer who were receiving chemotherapy were using marijuana, and the frequency was equal in early- and advanced-stage cancer groups. The risks versus benefits should be discussed with all patients who use marijuana.

Safakish, R., G. Ko, et al. (2020). "Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study." Pain Medicine.

To evaluate the short-term and long-term effects of plant-based medical cannabis in a chronic pain population over the course of one year.A longitudinal, prospective, 12-month observational study.Patients were recruited and treated at a clinic specializing in medical cannabis care from October 2015 to March 2019.A total of 751 chronic pain patients initiating medical cannabis treatment.Study participants completed the Brief Pain Inventory and the 12-item Short Form Survey (SF-12), as well as surveys on opioid medication use and adverse events, at baseline and once a month for 12 months.Medical cannabis treatment was associated with improvements in pain severity and interference (P &lt; 0.001) observed at one month and maintained over the 12-month observation period. Significant improvements were also observed in the SF-12 physical and mental health domains (P &lt; 0.002) starting at three months. Significant decreases in headaches, fatigue, anxiety, and nausea were observed after initiation of treatment (P ≤ 0.002). In patients who reported opioid medication use at baseline, there were significant reductions in oral morphine equivalent doses (P &lt; 0.0001), while correlates of pain were significantly improved by the end of the study observation period.Taken together, the findings of this study add to the cumulative evidence in support of plant-based medical cannabis as a safe and effective treatment option and potential opioid medication substitute or augmentation therapy for the management of symptoms and quality of life in chronic pain patients.

Saft, C., S. M. von Hein, et al. (2018). "Cannabinoids for Treatment of Dystonia in Huntington's

Disease." J Huntingtons Dis 7(2): 167-173.

BACKGROUND: Motor symptoms in Huntington's disease (HD) are heterogeneous with dystonia being described as a symptom with a very high prevalence not only in juvenile cases. OBJECTIVE: Treatment options for dystonia are limited. Cannabinoids have been described as a potential treatment for patients with dystonia of a different origin. Here, we present early onset HD patients with a marked improvement of motor symptoms mainly due to alleviation of dystonia due to treatment with cannabinoids. In addition we review the current literature concerning the use of cannabinoids in HD. METHOD: The Unified Huntington's Disease Rating Scale (UHDRS) motor score, including a chorea and dystonia subscore, was conducted before and after the start of cannabinoids in seven patients without any other changes in medication. RESULTS: The UHDRS motor score and the dystonia subscore (+/-SD) improved from 70.9 (25.5) to 60.6 (26.9) with a mean change of Research update –September 2018 10.3 [95% CI 6.0-14.6] and from 12.3 (4.0) to 8.0 (3.6) with a mean change of 4.3 [95% CI 2.3- 6.3], respectively (both p = 0.018). CONCLUSION: Improvement of motor symptoms, mainly dystonia, led to several relevant improvements from a global clinical perspective such as improvement of care, gait and fine motor skills and weight gain. Moreover, we observed changes in behavior with less irritability and apathy, as well as less hypersalivation in some cases.

Sagy, I., L. Bar-Lev Schleider, et al. (2019). "Safety and Efficacy of Medical Cannabis in Fibromyalgia." J Clin Med 8(6).

BACKGROUND: Chronic pain may be treated by medical cannabis. Yet, there is scarce evidence to support the role of medical cannabis in the treatment of fibromyalgia. The aim of the study was to investigate the characteristics, safety, and effectiveness of medical cannabis therapy for fibromyalgia. METHODS: A prospective observational study with six months follow-up period based on fibromyalgia patients who were willing to answer questionnaire in a specialized medical cannabis clinic between 2015 and 2017. RESULTS: Among the 367 fibromyalgia patients, the mean age was 52.9 +/- 15.1, of whom 301 (82.0%) were women. Twenty eight patients (7.6%) stopped the treatment prior to the six months follow-up. The six months response rate was 70.8%. Pain intensity (scale 0-10) reduced from a median of 9.0 at baseline to 5.0 (p < 0.001), and 194 patients (81.1%) achieved treatment response. In a multivariate analysis, age above 60 years (odds ratio [OR] 0.34, 95% C.I 0.16-0.72), concerns about cannabis treatment (OR 0.36, 95% C.I 0.16-0.80), spasticity (OR 2.26, 95% C.I 1.08-4.72), and previous use of cannabis (OR 2.46 95% C.I 1.06-5.74) were associated with treatment outcome. The most common adverse effects were mild and included dizziness (7.9%), dry mouth (6.7%), and gastrointestinal symptoms (5.4%). CONCLUSION: Medical cannabis appears to be a safe and effective alternative for the treatment of fibromyalgia symptoms. Standardization of treatment compounds and regimens are required.

Sagy, I., T. Peleg-Sagy, et al. (2018). "Ethical issues in medical cannabis use." European Journal of Internal Medicine **49**: 20-22.

The increasing use of medical cannabis (MC) in the past decade raises several ethical considerations for the clinician. Regulatory issues stem from a gap between MC registration and certification in each country. Professional issues derive from the lack of sufficient knowledge of MC characteristics and the intersection between the physician, the patient and commercial interests. Finally, there are medical and psychological implications which are related to the use of MC regimens. We will discuss these issues in the light of the current era, in which policy has rapidly shifted toward legalization of cannabis, which influences the decisions of both clinicians and patients.

Sałaga, M., R. Abalo, et al. (2017). Chapter 49 - Cannabis and Cannabinoids and the Effects on Gastrointestinal Function: An Overview A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 471-480.

Abstract For centuries, cannabis has been used to treat gastrointestinal (GI) diseases that range from enteric infections and inflammatory conditions to motility disorders, emesis, and abdominal pain. This chapter provides an overview of the role of exo- and endogenous cannabinoids in gut homeostasis. We will focus on pharmacological actions of cannabinoids in the GI tract, both in physiological and pathophysiological conditions. Furthermore, we will refer to the localization of the endogenous cannabinoid system (ECS) in the gut, and its organization at the molecular level, as well as to the endocannabinoid degradation pathways. Since ECS is strongly involved in pain signaling, we will also discuss potential control of abdominal pain with cannabinoids. Finally, we will take a look into the use of cannabinoid-derived and ECS-targeting drugs for the treatment of GI diseases.

Salottolo, K., L. Peck, et al. (2018). "The grass is not always greener: a multi-institutional pilot study of marijuana use and acute pain management following traumatic injury." Patient Saf Surg 12: 16.

Background: Widespread legislative efforts to legalize marijuana have increased the prevalence of marijuana use and abuse. The effects of marijuana on pain tolerance and analgesic pain management in the acute pain setting have not been reported. Although marijuana has been shown to have antinociceptive effects and is approved for medical use to treat chronic pain, anecdotal evidence suggests marijuana users admitted with traumatic injuries experience poorer pain control than patients who do not use marijuana. We hypothesized that marijuana users would report higher pain scores and require more opioid analgesia following traumatic injury. Methods: This retrospective pilot study included all patients involved in motor vehicle crashes, consecutively admitted to four trauma centers from 1/1/2016-4/30/2016. Marijuana status was examined as non-use and use, and was further categorized as chronic and episodic use. We performed a repeated measures mixed model to examine the association between marijuana use and a) average daily opioid consumption and b) average daily pain scores (scale 0-10). Opioid analgesics were converted to be equianalgesic to 1 mg IV hydromorphone. Results: Marijuana use was reported in 21% (54/261), of which 30% reported chronic use (16/54). Marijuana use was reported more frequently in Colorado hospitals (23-29%) compared to the hospital in Texas (6%). Drug use with other prescription/street drugs was reported in 9% of patients. Other drug use was a significant effect modifier and results were presented after stratification by drug use. After adjustment, marijuana users who did not use other drugs consumed significantly more opioids (7.6 mg vs. 5.6 mg, p < 0.001) and reported higher pain scores (4.9 vs. 4.2, p < 0.001) than non-marijuana users. Conversely, in patients who used other drugs, there were no differences in opioid consumption (5.6 mg vs. 6.1 mg, p = 0.70) or pain scores (5.3 vs. 6.0, p = 0.07) with marijuana use compared to non-use, after adjustment. Chronic marijuana use was associated with significantly higher opioid consumption compared to episodic marijuana use in concomitant drug users (11.3 mg vs. 4.4 mg, p = 0.008) but was similar in non-drug users (p = 0.41). Conclusion: These preliminary data suggest that marijuana use, especially chronic use, may affect pain response to injury by requiring greater use of opioid analgesia. These results were less pronounced in patients who used other drugs.

Sands, T. T., S. Rahdari, et al. (2019). "Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US." CNS Drugs 33(1): 47-60.

BACKGROUND: Purified cannabidiol is a new antiepileptic drug that has recently been approved for use in patients with Lennox-Gastaut and Dravet syndromes, but most published studies have not extended beyond 12-16 weeks.   
OBJECTIVE: The objective of this study was to evaluate the long-term safety, tolerability, and efficacy of cannabidiol in children with epilepsy.  
METHODS: Patients aged 1-17 years with refractory epilepsy were enrolled in an open-label prospective study through individual patient and expanded access programs between April 2013 and December 2014. Seizure types were video-electroencephalogram confirmed prior to enrollment. After a 28-day evaluation period, during which baseline seizure frequency was assessed, cannabidiol was given as add-on therapy at 5 mg/kg/day and titrated weekly by 5-mg/kg increments to a dose of 25 mg/kg/day. Blood tests were performed at baseline, after 1, 2, and 3 months, and every 3 months thereafter. Trough concentrations of concomitant antiepileptic drugs were measured at baseline, after 1, 2, and 3 months of therapy, and as clinically indicated afterwards. Concomitant antiepileptic drugs, ketogenic diet ratio, and vagal nerve stimulator settings remained unchanged during the baseline period and the first 3 months of treatment, unless there was a significant increase in plasma concentrations. Seizure frequency was reported daily in seizure diaries by parents or caregivers. Clinical assessments occurred after 15 days of treatment, at 1 month, at 3 months, and every 3 months thereafter. Diaries of seizure frequency and adverse events were reviewed at each visit. The primary efficacy outcome was a reduction in seizure frequency and responders were defined as those patients achieving a > 50% reduction in motor seizures.  
RESULTS: Twenty-six children were enrolled. Most had genetic epilepsies with daily or weekly seizures and multiple seizure types. All were refractory to prior antiepileptic drugs (range 4-11, mean 7), and were taking two antiepileptic drugs on average. Duration of therapy ranged from 4 to 53 months (mean 21 months). Adverse events were reported in 21 patients (80.8%), including reduced appetite in ten (38.4%), diarrhea in nine (34.6%), and weight loss in eight (30.7%). Four (15.4%) had changes in antiepileptic drug concentrations and three had elevated aspartate aminotransferase and alanine aminotransferase levels when cannabidiol was administered together with valproate. Serious adverse events, reported in six patients (23.1%), included status epilepticus in three, catatonia in two, and hypoalbuminemia in one. Fifteen patients (57.7%) discontinued cannabidiol for lack of efficacy, one because of status epilepticus, and one for severe weight loss. The retention rate declined rapidly in the first 6 months and more gradually thereafter. At 24 months, the number of patients continuing cannabidiol as adjunctive therapy was nine of the original 26 (34.6%). Of these patients, seven (26.9%) had a sustained > 50% reduction in motor seizures, including three (11.5%) who remain seizure free.   
CONCLUSION: Over a 4-year period, cannabidiol was effective in 26.9% of children with otherwise refractory epilepsy. It was well tolerated in about 20% of patients, but 80.8% had adverse events, including 23.1% with serious adverse events. Decreased appetite and diarrhea were frequent along with weight loss that became evident only later in the treatment.

Sarzi-Puttini, P., A. Batticciotto, et al. (2019). "Medical cannabis and cannabinoids in rheumatology: where are we now?" Expert Review of Clinical Immunology: null-null.

Introduction: Clinicians involved in pain management can finally include cannabis or cannabis-related products in their therapeutic armamentarium as a growing number of countries have approved them for pain relief. Despite the several benefits attributed to analgesic, anti-inflammatory and immunomodulatory properties of cannabinoids, there are still significant areas of uncertainty concerning their use in many fields of medicine. The biosynthesis and inactivation of cannabinoids are regulated by a complex signaling system of cannabinoid receptors, endocannabinoids (the endogenous ligands of cannabinoid receptors) and enzymes, with a variety of interactions with neuroendocrinological and immunological systems.

Areas covered: A review of studies carried out during clinical development of cannabis and cannabis medical products in systemic rheumatic diseases was performed, highlighting the aspects that we believe to be relevant to clinical practice.

Expert opinion: The growing public opinion, pushing towards the legalization of the use of cannabis in chronic pain and various rheumatological conditions, makes it necessary to have educational programs that modify the concerns and widespread preconceptions related to this topic in the medical community by increasing confidence. More extensive basic and clinical research on the mechanisms and clinical utility of cannabis and derivatives in various diseases and their long-term side effects is necessary.

Scharmer, C., B. R. Altman, et al. (2020). "Expectancies about the Effects of Cannabis Use on Eating Disorder Symptoms." Subst Use Misuse: 1-9.

Background: Substance use, specifically cannabis use, is common among individuals with eating disorder (ED) symptoms; however, few studies have specifically explored the relation between EDs and cannabis use. Purpose: The present study examined expectancies about the impact of cannabis on cognitive, affective and behavioral ED symptoms. Additionally, this study explored associations between cannabis-related expectancies, cannabis use and cannabis-related problems. Methods: Cannabis users with ED symptoms (N = 137) reported on frequency of cannabis use, cannabis-related problems and expectancies about the impact of cannabis on ED symptoms, Results: Participants expected cannabis to decrease restrictive eating, compensatory behaviors, and preoccupation with body shape and weight and fear of eating and weight gain. In contrast, cannabis was expected to increase binge-eating behaviors. Expectancies about the impact of cannabis use on ED symptoms were not associated with more frequent cannabis use nor were they associated with cannabis-related problems. Conclusions: These findings suggest that individuals believe cannabis will improve some ED symptoms; however, these expected improvements are not associated with increased cannabis use and problems. Future research should examine cannabis expectancies in clinical populations and should further explore the association between cannabis expectancies, use, and ED symptoms longitudinally.

Sexton, M. (2020). "Cannabis in the Time of Coronavirus Disease 2019: The Yin and Yang of the Endocannabinoid System in Immunocompetence." J Altern Complement Med **26**(6): 444-448.

Editor's Note: For those whose response to COVID-19 includes exploring beyond vaccines, conventional pharmaceuticals, and the watchful or healthy waiting until such tools might arrive, interest in cannabinoids has been high - and controversial. It has already stimulated one journal, the Liebert Cannabis and Cannabinoid Research, to issue a call for papers on COVID-19. The unique place of cannabis in the culture seems to always mark the herb with an exponential asterisk whenever basketed with the other natural health strategies that are both widely used, and as broadly derided. In this invited commentary, JACM Editorial Board member Michelle Sexton, ND starts by describing the multiple immune modulating effects associated with the herb. The University of California San Diego Assistant Adjunct Professor in Anesthesiology then asks: "Given these effects, can phytocannabinoids be either helpful, or harmful for immune competency, in the context of the current COVID-19 pandemic?" A skilled edge-walker, Sexton lets the research fall where it may in wending a path through this evidentiary maze. -John Weeks, Editor-in-Chief, JACM.

Shannon, S., N. Lewis, et al. (2019). "Cannabidiol in Anxiety and Sleep: A Large Case Series." The Permanente journal **23**: 18-041.

CONTEXT: Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a "high." A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature. OBJECTIVE: To determine whether CBD helps improve sleep and/or anxiety in a clinical population. DESIGN: A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients. MAIN OUTCOME MEASURES: Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment. RESULTS: The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients. CONCLUSION: Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.

Shover, C. L., C. S. Davis, et al. (2019). "Association between medical cannabis laws and opioid overdose mortality has reversed over time." Proceedings of the National Academy of Sciences 116(26): 12624.

Medical cannabis has been touted as a solution to the US opioid overdose crisis since Bachhuber et al. [M. A. Bachhuber, B. Saloner, C. O. Cunningham, C. L. Barry, JAMA Intern. Med. 174, 1668–1673] found that from 1999 to 2010 states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality. That research received substantial attention in the scientific literature and popular press and served as a talking point for the cannabis industry and its advocates, despite caveats from the authors and others to exercise caution when using ecological correlations to draw causal, individual-level conclusions. In this study, we used the same methods to extend Bachhuber et al.’s analysis through 2017. Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23% and remained positive after accounting for recreational cannabis laws. We also uncovered no evidence that either broader (recreational) or more restrictive (low-tetrahydrocannabinol) cannabis laws were associated with changes in opioid overdose mortality. We find it unlikely that medical cannabis—used by about 2.5% of the US population—has exerted large conflicting effects on opioid overdose mortality. A more plausible interpretation is that this association is spurious. Moreover, if such relationships do exist, they cannot be rigorously discerned with aggregate data. Research into therapeutic potential of cannabis should continue, but the claim that enacting medical cannabis laws will reduce opioid overdose death should be met with skepticism.A 2014 study by Bachhuber et al. (1) created a sensation by showing that state medical cannabis laws were associated with lower-than-expected opioid overdose mortality rates from 1999 to 2010. … ↵1To whom correspondence may be addressed. Email: clshover{at}stanford.edu.

Schwartz, D. A. (2018). "Cannabis and the Lung." International Journal of Mental Health and Addiction **16**(4): 797-800.

While most cannabis use involves inhalation of the fumes from combustion, other routes of administration are also common but the consequences of these routes of exposure are less well known than from that of smoking. It is clear that prolonged use of cannabis causes chronic bronchitis and airflow obstruction in heavy users. However, there is a need to further understand the lung biology influenced by cannabis use, the potential for lung carcinogenesis, the effects of high THC products, and the health effects of different routes of administration. This review summarizes the present state of knowledge with regard to irritation and long-term effects on the lung and bronchial tissues.

Schröder, N., V. K. da Silva, et al. (2017). Chapter 83 - Cannabidiol and Neuroprotection: Evidence from Preclinical Studies A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 802-812.

Abstract Cannabidiol (CBD) is the main nonpsychotropic constituent of Cannabis sativa. In recent years, preclinical in vitro and in vivo studies have investigated the potential of CBD in experimental models focusing on neurodegeneration. The purpose of this chapter is to provide a comprehensive overview on the main studies reporting the effects of CBD in the context of hypoxic-ischemic injury and Alzheimer’s disease, as well as other relevant experimental models of neurodegeneration, and to discuss its putative mechanisms. Evidence indicates that CBD displays antioxidant, antiinflammatory, and antiapoptotic properties, and can also prevent excitotoxic damage, and protect mitochondria against toxins. Accordingly, CBD was shown to ameliorate damage observed in animal models of neurodegeneration associated to hypoxic-ischemic brain injury, multiple sclerosis, brain iron overload, Alzheimer’s, Parkinson’s, and Huntington’s disease. Thus, CBD may constitute a promising therapeutic agent for the prevention/treatment of neurodegenerative disorders.

Scott, J. C., S. T. Slomiak, et al. (2018). "Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis." JAMA Psychiatry **75**(6): 585- 595.

Importance: Substantial shifts in perception and policy regarding cannabis have recently occurred, with use of cannabis increasing while its perceived harm decreases. One possible risk of increased cannabis use is poorer cognitive functioning, especially in youth. Objective: To provide the first quantitative synthesis of the literature examining cannabis and cognitive functioning in adolescents and young adults (with a mean age of 26 years and younger). Data Sources: PubMed, PsycInfo, Academic Search Premier, Scopus, and bibliographies of relevant reviews were searched for peer-reviewed, English-language studies from the date.   
Research update –September 2018 the databases began through May 2017. Study Selection: Consensus criteria were used to determine study inclusion through abstract and manuscript review. Data Extraction and Synthesis: This study followed Meta-analysis of Observational Studies in Epidemiology guidelines. Effect size estimates were calculated using multivariate mixed-effects models for cognitive functioning outcomes classified into 10 domains. Main Outcomes and Measures: Results from neurocognitive tests administered in cross-sectional studies were primary outcomes, and we examined the influence of a priori explanatory variables on variability in effect size. Results: Sixty-nine studies of 2152 cannabis users (mean [SD] age, 20.6 [2.8] years; 1472 [68.4%] male) and 6575 comparison participants with minimal cannabis exposure were included (mean [SD] age, 20.8 [3.4]; 3669 [55.8%] male). Results indicated a small overall effect size (presented as mean d) for reduced cognitive functioning associated with frequent or heavy cannabis use (d, -0.25; 95% CI, -0.32 to -0.17; P < .001). The magnitude of effect sizes did not vary by sample age or age at cannabis use onset. However, studies requiring an abstinence period longer than 72 hours (15 studies; n = 928) had an overall effect size (d, -0.08; 95% CI, -0.22 to 0.07) that was not significantly different from 0 and smaller than studies with less stringent abstinence criteria (54 studies; n = 7799; d, - 0.30; 95% CI, -0.37 to -0.22; P = .01). Conclusions and Relevance: Associations between cannabis use and cognitive functioning in cross-sectional studies of adolescents and young adults are small and may be of questionable clinical importance for most individuals. Furthermore, abstinence of longer than 72 hours diminishes cognitive deficits associated with cannabis use. Although other outcomes (eg, psychosis) were not examined in the included studies, results indicate that previous studies of cannabis in youth may have overstated the magnitude and persistence of cognitive deficits associated with use. Reported deficits may reflect residual effects from acute use or withdrawal. Future studies should examine individual differences in susceptibility to cannabis-associated cognitive dysfunction

Selvarajah, D., R. Gandhi, et al. (2017). Chapter 94 - Cannabinoids and Their Effects on Painful Neuropathy A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 905-916.

Abstract Chronic neuropathic pain is a common, disabling condition that is often challenging to manage effectively. Unfortunately, most current pharmacological treatments are often ineffective and their use is limited by intolerable side effects. There is ample anecdotal and preclinical trial evidence supporting the pain relieving role of cannabinoids. This analgesic property of cannabinoids is thought to be mediated via receptors in three key areas involved in pain control (peripheral nerves, spinal cord, and brain). Cannabinoids have been evaluated in a number of clinical pain trials and exhibit their greatest efficacy when employed in the management of neuropathic pain. However, the outcomes in the limited range of clinical trials conducted thus far have been largely disappointing, with modest effect sizes not dissimilar to many of the currently used neuropathic pain treatments. Further clinical trials are needed to fully examine the long-term safety and efficacy on pain and functional measures of these compounds.

Sherman, J. J., D. M. Riche, et al. (2019). "Cannabidiol Oral Solution: Challenges as a Treatment for Seizure Syndromes." The Journal for Nurse Practitioners.

Objective To review the available literature associated with cannabidiol oral solution. Data Sources A PubMed search (1963 to August 2018) using the terms “cannabidiol oral solution” was conducted. Study Selection and Data Extraction Evaluations of cannabidiol oral solution were eligible for inclusion. Data Synthesis Three clinical trials were evaluated, 2 for Lennox-Gastaut syndrome and 1 for Dravet syndrome. After 14 weeks, the percentage of monthly drop seizures was reduced by 43.9% in the cannabidiol and 21.8% in the placebo groups. Conclusions Cannabidiol oral solution is safe and effective add-on therapy for treatment-resistant seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.

Sideris, A., F. Khan, et al. (2018). "New York Physicians' Perspectives and Knowledge of the State Medical Marijuana Program." Cannabis and Cannabinoid Research **3**(1): 74-84.

Abstract Introduction: In 2014, New York (NY) became the 23rd state to legalize medical marijuana (MMJ). The purpose of this survey was to collect data about practicing NY physicians' comfort level, opinions, and experience in recommending or supporting patient use of MMJ. Materials and Methods: An anonymous web-based survey was distributed to medical societies and to academic departments in medical schools within NY. Results: A total of 164 responses were analyzed. Physician participants were primarily located in New York City and surrounding areas. The majority (71%) agreed that MMJ should be an option available to patients. Most respondents were not registered to certify MMJ in NY, but were willing to refer patients to registered physicians. Common reasons for not registering included specialty and federal status of cannabis. More than 75% reported having patients who used cannabis for symptom control, and 50% reported having patients who inquired about MMJ within the past year. Most respondents are willing to discuss MMJ with their patients, but had little familiarity with the state program and a modest knowledge of the endocannabinoid system. Pain was a common symptom for which cannabis was recommended by registered physicians (69%) and purportedly used by patients (83%). Most respondents would consider MMJ as an adjuvant to opioids, and 84% believed opioids have greater risks than MMJ. Conclusion: Given that the majority of surveyed physicians support MMJ as an option for patients, few are registered and have adequate knowledge of MMJ. Although our study sample is small and geographically limited, our survey results highlight key physician issues that are likely applicable to practitioners in other states. Concerted efforts are needed at the federal, state, and academic levels to provide practitioners with evidence-based guidelines for the safe use of MMJ.

Singer, M., A. Azim, et al. (2017). "How does marijuana affect outcomes after trauma in ICU patients? A propensity-matched analysis." Journal of Trauma and Acute Care Surgery **83**(5): 846-849.

INTRODUCTION In the United States, marijuana abuse and dependence are becoming more prevalent among adult and adolescent trauma patients. Unlike several studies that focus on the effects of marijuana on the outcomes of diseases, our aim was to assess the relationship between a positive toxicology screen for marijuana and mortality in such patients. METHODS A 5-year (2008–2012) analysis of adult trauma patients (older than 18 years old) in Arizona State Trauma Registry. We included patients admitted to the intensive care unit (ICU) with a positive toxicology screen for marijuana. We excluded patients with positive alcohol or other substance screening. Outcome measures were mortality, ventilator days, ICU, and hospital length of stay. We matched patients who tested positive for marijuana (marijuana positive) to those who tested negative (marijuana negative) using propensity score matching in a 1:1 ratio controlling for age, injury severity score, and Glasgow Coma Scale. RESULTS We included a total of 28,813 patients, of which 2,678 were matched (1,339, marijuana positive; 1,339, marijuana negative). The rate of positive screening for marijuana was 7.4% (2,127/28,813). Mean age was 31 ± 9 years, and injury severity score was 13 (8–20). There was no difference between the two groups in hospital (6.4 days vs. 5.4 days, p = 0.08) or ICU (3 days vs. 4 days, p = 0.43) length of stay. Of the marijuana-positive patients, 55.3% received mechanical ventilation, while 32% of marijuana-negative patients received mechanical ventilation (p < 0.001). On subanalysis of patients who received mechanical ventilation, the marijuana-positive patients had a higher number of ventilator days (2 days vs. 1 day, p = 0.02) and a lower mortality rate (7.3% vs. 16.1%, p < 0.001) than those who were marijuana negative. CONCLUSION A positive marijuana screen is associated with decreased mortality in adult trauma patients admitted to the ICU. This association warrants further investigation of the possible physiologic effects of marijuana in trauma patients. LEVEL OF EVIDENCE Prognostic studies, level III.

Singh, A., S. Saluja, et al. (2018). "Cardiovascular Complications of Marijuana and Related Substances: A Review." Cardiol Ther **7**(1): 45-59.

The recreational use of cannabis has sharply increased in recent years in parallel with its legalization and decriminalization in several countries. Commonly, the traditional cannabis has been replaced by potent synthetic cannabinoids and cannabimimetics in various forms. Despite overwhelming public perception of the safety of these substances, an increasing number of serious cardiovascular adverse events have been reported in temporal relation to recreational cannabis use. These have included sudden cardiac death, vascular (coronary, cerebral and peripheral) events, arrhythmias and stress cardiomyopathy among others. Many of the victims of these events are relatively young men with few if any cardiovascular risk factors. However, there are reasons to believe that older individuals and those with risk factors for or established cardiovascular disease are at even higher danger of such events following exposure to cannabis. The pathophysiological basis of these events is not fully understood and likely encompasses a complex interaction between the active ingredients (particularly the major cannabinoid, Delta(9)-tetrahydrocannabinol), and the endocannabinoid system, autonomic nervous system, as well as other receptor and non-receptor mediated pathways. Other complicating factors include opposing physiologic effects of other cannabinoids (predominantly cannabidiol), presence of regulatory proteins that act as metabolizing enzymes, binding molecules, or ligands, as well as functional polymorphisms of target receptors. Tolerance to the effects of cannabis may also develop on repeated exposures at least in part due to receptor downregulation or desensitization. Moreover, effects of cannabis may be enhanced or altered by concomitant use of other illicit drugs or medications used for treatment of established cardiovascular diseases.  
Research update –September 2018 considerations, it is expected that the current cannabis epidemic would add significantly to the universal burden of cardiovascular diseases.

Shaikh, A. and S. Money (2019). "Cannabinoids and Pain Management: an Insight into Recent Advancements." Current Emergency and Hospital Medicine Reports.

This review discusses the recent advancements in research on Cannabinoids’ role in pain, including its use in cancer pain, neuropathic pain, fibromyalgia, headache, visceral pain, postoperative and failed back pain management, and concurrent use with opioids.

Skinner, C. M., I. Nookaew, et al. (2020). "Potential Probiotic or Trigger of Gut Inflammation - The Janus-Faced Nature of Cannabidiol-Rich Cannabis Extract." J Diet Suppl: 1-18.

Cannabidiol (CBD) is the major non-psychotropic phytocannabinoid present in Cannabis sativa. In 2018, Congress designated certain C. sativa plant material as "hemp," thus removing it from the DEA's list of controlled substances. As a result, CBD-containing hemp extracts and other CBD products are now widely available and heavily marketed, yet their FDA regulatory status is still hotly debated. The goal of this study was to investigate the effects of a cannabidiol-rich cannabis extract (CRCE) on the gut microbiome and associated histomorphological and molecular changes in the mouse gut mucosa. Male C57BL6/J mice were gavaged with either 0, 61.5, 184.5, or 615 mg/kg/bw of CRCE in sesame oil for 2 weeks (Mon-Fri). Substantial CRCE-induced increases in the relative abundance of A. muciniphila, a bacterial species currently accepted as probiotic, was observed in fecal samples at all doses. This was paralleled by decreases in the relative abundance of other gut bacterial species. Coincident with the observed changes in gut ecology were multiple pro-inflammatory responses, including increased expression of cytokines and chemokines-Il1ß, Cxcl1, and Cxcl2 in the colon tissue. Furthermore, dramatic increases in the relative abundance of A. muciniphila significantly decreased expression of Muc2-a gene intimately associated with gut integrity. Taken together, these findings raise concerns about the safety of long-term CBD usage and underline the need for additional well-designed studies into its tolerability and efficacy.

Slomski, A. (2017). "Fewer seizures with cannabidiol in catastrophic epilepsy." JAMA **318**(4): 323-323.

The study randomly assigned 120 children and young adults with the syndrome and drug-resistant seizures to receive either cannabidiol (20 mg/kg of body weight per day) or placebo, in addition to standard antiepileptic treatment.

Smith, R. A. (2020). "THE EFFECTS OF MEDICAL MARIJUANA DISPENSARIES ON ADVERSE OPIOID OUTCOMES." Economic Inquiry **58**(2): 569-588.

As more states enact laws liberalizing marijuana use and the U.S. opioid epidemic surges to unprecedented levels, understanding the relationship between marijuana and opioids is growing increasingly important. Using a unique self-constructed marijuana dispensary dataset, I estimate the impact of increased marijuana access on opioid-related harms. I exploit within- and across-state variation in dispensary openings and find county-level prescription opioid-related fatalities decline by 11% following the opening a dispensary. The estimated dispensary effects are qualitatively similar for opioid-related admissions to treatment facilities. These results are strongest for males and suggest a substitutability between marijuana and opioids.

Socías, M. E., T. Kerr, et al. (2017). "Intentional cannabis use to reduce crack cocaine use in a Canadian setting: A longitudinal analysis." Addictive Behaviors **72**: 138-143.

AbstractBackground No effective pharmacotherapies exist for the treatment of crack cocaine use disorders. Emerging data suggests that cannabinoids may play a role in reducing cocaine-related craving symptoms. This study investigated the intentional use of cannabis to reduce crack use among people who use illicit drugs (PWUD). Methods Data were drawn from three prospective cohorts of PWUD in Vancouver, Canada. Using data from participants reporting intentional cannabis use to control crack use, we used generalized linear mixed-effects modeling to estimate the independent effect of three pre-defined intentional cannabis use periods (i.e., before, during and after first reported intentional use to reduce crack use) on frequency of crack use. Results Between 2012 and 2015, 122 participants reported using cannabis to reduce crack use, contributing a total of 620 observations. In adjusted analyses, compared to before periods, after periods were associated with reduced frequency of crack use (Adjusted Odds Ratio [AOR] = 1.89, 95% Confidence Interval [CI]: 1.02–3.45), but not the intentional use periods (AOR = 0.85, 95% CI: 0.51–1.41). Frequency of cannabis use in after periods was higher than in before periods (AOR = 4.72, 95% CI: 2.47–8.99), and showed a tendency to lower frequency than in intentional cannabis use periods (AOR = 0.56, 95% CI: 0.32–1.01). Conclusions A period of intentional cannabis use to reduce crack use was associated with decreased frequency of crack use in subsequent periods among PWUD. Further clinical research to assess the potential of cannabinoids for the treatment of crack use disorders is warranted.

Solowij, N., P. Galettis, et al. (2018). "Second-Hand Exposure of Staff Administering Vaporised Cannabinoid Products to Patients in a Hospital Setting." Drugs in R&D **18** (1): 41-44.

In many health settings, administration of medicinal cannabis poses significant implementation barriers including drug storage and safety for administering staff and surrounding patients. Different modes of administration also provide different yet potentially significant issues. One route that has become of clinical interest owing to the rapid onset of action and patient control of the inhaled amount (via breath timing and depth) is that of vaporisation of cannabinoid products. Although requiring a registered therapeutic device for administration, this is a relatively safe method of intrapulmonary administration that may be particularly useful for patients with difficulty swallowing, and for those in whom higher concentrations of cannabinoids are needed quickly. A particular concern expressed to researchers undertaking clinical trials in the hospital is that other patients, nurses, and clinical or research staff may be exposed to second-hand vapours in the course of administering vaporised products to patients.

Sorosina, M., F. Clarelli, et al. (2018). "Clinical response to Nabiximols correlates with the downregulation of immune pathways in multiple sclerosis." Eur J Neurol **25** (7): 934-e970.

BACKGROUND AND PURPOSE: Nabiximols (Sativex((R)) ) is a cannabinoid-based compound used for the treatment of moderate to severe spasticity in multiple sclerosis (MS). The aim of the study was to investigate the effect of the administration of Nabiximols on blood transcriptome profile of patients with MS and to interpret it in the context of pathways and networks. METHODS: Whole-genome expression profiling was performed in whole blood of 33 subjects with MS at baseline and after 4 weeks of drug treatment. Patients were classified as responders (n = 19) and non-responders (n = 14). Pathway and network analyses on genes modulated by the drug were performed, followed by in vitro stimulation of peripheral blood mononuclear cells with pro-inflammatory agents to support the immunomodulatory properties of the drug. RESULTS: Individual effect size was modest; however, we observed a downregulation of several immune-related pathways after 4 weeks of treatment, which was more pronounced when restricting analyses to responders. Interesting hub molecules functionally related to the immune system emerged from network analysis, including NFKB1, FYN, MAP14 and TP53. The immunomodulatory properties of the drug were confirmed through in vitro assays in peripheral blood mononuclear cells collected from patients with MS. CONCLUSIONS: Our findings support the immunomodulatory activity of cannabinoids in patients with MS. Further studies in more specific cell types are needed to refine these results.

Spindle, T. R., E. J. Cone, et al. (2020). "Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis." J Anal Toxicol **44**(2): 109-125.

Cannabis products in which cannabidiol (CBD) is the primary chemical constituent (CBD-dominant) are increasingly popular and widely available. The impact of CBD exposure on urine drug testing has not been well studied. This study characterized the urinary pharmacokinetic profile of 100-mg oral and vaporized CBD, vaporized CBD-dominant cannabis (100-mg CBD; 3.7-mg ∆9-THC) and placebo in healthy adults (n = 6) using a within-subjects crossover design. Urine specimens were collected before and for 5 days after drug administration. Immunoassay (IA) screening (cutoffs of 20, 50 and 100 ng/mL) and LC-MS-MS confirmatory tests (cutoff of 15 ng/mL) for 11-nor-9-carboxy-∆9-tetrahydrocannabinol (∆9-THCCOOH) were performed; urine was also analyzed for CBD and other cannabinoids. Urinary concentrations of CBD were higher after oral (mean Cmax: 776 ng/mL) versus vaporized CBD (mean Cmax: 261 ng/mL). CBD concentrations peaked 5 h after oral CBD ingestion and within 1 h after inhalation of vaporized CBD. After pure CBD administration, only 1 out of 218 urine specimens screened positive for ∆9-THCCOOH (20-ng/mL IA cutoff) and no specimens exceeded the 15-ng/mL confirmatory cutoff. After inhalation of CBD-dominant cannabis vapor, nine samples screened positive at the 20-ng/mL IA cutoff, and two of those samples screened positive at the 50-ng/mL IA cutoff. Four samples that screened positive (two at 20 ng/mL and two at 50 ng/mL) confirmed positive with concentrations of ∆9-THCCOOH exceeding 15 ng/mL. These data indicate that acute dosing of pure CBD will not result in a positive urine drug test using current federal workplace drug testing guidelines (50-ng/mL IA cutoff with 15-ng/mL confirmatory cutoff). However, CBD products that also contain ∆9-THC may produce positive urine results for ∆9-THCCOOH. Accurate labeling and regulation of ∆9-THC content in CBD/hemp products are needed to prevent unexpected positive drug tests and unintended drug effects.

St Pierre, M., E. B. Russo, et al. (2020). "No Evidence of Altered Reactivity to Experimentally Induced Pain Among Regular Cannabis Users." Clin J Pain **36**(8): 589-593.

OBJECTIVES: Recent years have seen an increase in the adoption of cannabinoid medicines, which have demonstrated effectiveness for the treatment of chronic pain. However, the extent to which frequent cannabis use (CU) influences sensitivity to acute pain has not been systematically examined. Such a determination is clinically relevant in light of hypersensitivity to pain associated with prolonged use of other analgesics such as opioids, and reports of increased pain sensitivity to experimentally induced pain during acute cannabis intoxication. This study explored differences in measures of pain intensity and tolerance. The authors hypothesized that individuals who report frequent CU would demonstrate greater experimental pain sensitivity. MATERIALS AND METHODS: Frequent cannabis users (≥3× per week; n=40) and nonusers (n=40) were compared on pain sensitivity, pain tolerance, and pain intensity in response to a cold-pressor task. Group differences were examined. RESULTS: Frequent CU was not associated with hyperalgesia as cannabis users and nonusers did not exhibit differences on measures of pain tolerance (t (78)=-0.05; P=0.96), sensitivity (t (78)=-0.83; P=0.41), or intensity (t (78)=0.36; P=0.72). DISCUSSION: Frequent cannabis users did not demonstrate hyperalgesia. This finding should help to inform evaluations of the relative harms and benefits of cannabis analgesic therapies.

Stark, T., M. Di Bartolomeo, et al. (2020). "Altered dopamine D3 receptor gene expression in MAM model of schizophrenia is reversed by peripubertal cannabidiol treatment." Biochem Pharmacol **177**: 114004.

Gestational methylazoxymethanol acetate (MAM) treatment produces offspring with adult phenotype relevant to schizophrenia, including positive- and negative-like symptoms, cognitive deficits, dopaminergic dysfunction, structural and functional abnormalities. Here we show that adult rats prenatally treated with MAM at gestational day 17 display significant increase in dopamine D3 receptor (D3) mRNA expression in prefrontal cortex (PFC), hippocampus and nucleus accumbens, accompanied by increased expression of dopamine D2 receptor (D2) mRNA exclusively in the PFC. Furthermore, a significant change in the blood perfusion at the level of the circle of Willis and hippocampus, paralleled by the enlargement of lateral ventricles, was also detected by magnetic resonance imaging (MRI) techniques. Peripubertal treatment with the non-euphoric phytocannabinoid cannabidiol (30 mg/kg) from postnatal day (PND) 19 to PND 39 was able to reverse in MAM exposed rats: i) the up-regulation of the dopamine D3 receptor mRNA (only partially prevented by haloperidol 0.6 mg/kg/day); and ii) the regional blood flow changes in MAM exposed rats. Molecular modelling predicted that cannabidiol could bind preferentially to dopamine D3 receptor, where it may act as a partial agonist according to conformation of ionic-lock, which is highly conserved in GPCRs. In summary, our results demonstrate that the mRNA expression of both dopamine D2 and D3 receptors is altered in the MAM model; however only the transcript levels of D3 are affected by cannabidiol treatment, likely suggesting that this gene might not only contribute to the schizophrenia symptoms but also represent an unexplored target for the antipsychotic activity of cannabidiol.

Starowicz, K. and D. P. Finn (2017). Chapter Thirteen - Cannabinoids and Pain: Sites and Mechanisms of Action. Advances in Pharmacology. D. Kendall and S. P. H. Alexander, Academic Press. **80:** 437-475.

The endocannabinoid system, consisting of the cannabinoid1 receptor (CB1R) and cannabinoid2 receptor (CB2R), endogenous cannabinoid ligands (endocannabinoids), and metabolizing enzymes, is present throughout the pain pathways. Endocannabinoids, phytocannabinoids, and synthetic cannabinoid receptor agonists have antinociceptive effects in animal models of acute, inflammatory, and neuropathic pain. CB1R and CB2R located at peripheral, spinal, or supraspinal sites are important targets mediating these antinociceptive effects. The mechanisms underlying the analgesic effects of cannabinoids likely include inhibition of presynaptic neurotransmitter and neuropeptide release, modulation of postsynaptic neuronal excitability, activation of the descending inhibitory pain pathway, and reductions in neuroinflammatory signaling. Strategies to dissociate the psychoactive effects of cannabinoids from their analgesic effects have focused on peripherally restricted CB1R agonists, CB2R agonists, inhibitors of endocannabinoid catabolism or uptake, and modulation of other non-CB1R/non-CB2R targets of cannabinoids including TRPV1, GPR55, and PPARs. The large body of preclinical evidence in support of cannabinoids as potential analgesic agents is supported by clinical studies demonstrating their efficacy across a variety of pain disorders.

Starrels, J. L., S. R. Young, et al. (2020). "Disagreement and Uncertainty Among Experts About how to Respond to Marijuana Use in Patients on Long-term Opioids for Chronic Pain: Results of a Delphi Study." Pain Med **21**(2): 247-254.

BACKGROUND: Marijuana use is common among patients on long-term opioid therapy (LTOT) for chronic pain, but there is a lack of evidence to guide clinicians' response. OBJECTIVE: To generate expert consensus about responding to marijuana use among patients on LTOT. DESIGN: Analysis from an online Delphi study. SETTING/SUBJECTS: Clinician experts in pain and opioid management across the United States. METHODS: Participants generated management strategies in response to marijuana use without distinction between medical and nonmedical use, then rated the importance of each management strategy from 1 (not at all important) to 9 (extremely important). A priori rules for consensus were established, and disagreement was explored using cases. Thematic analysis of free-text responses examined factors that influenced participants' decision-making. RESULTS: Of 42 participants, 64% were internal medicine physicians. There was consensus that it is not important to taper opioids as an initial response to marijuana use. There was disagreement about the importance of tapering opioids if there is a pattern of repeated marijuana use without clinical suspicion for a cannabis use disorder (CUD) and consensus that tapering is of uncertain importance if there is suspicion for CUD. Three themes influenced experts' perceptions of the importance of tapering: 1) benefits and harms of marijuana for the individual patient, 2) a spectrum of belief about the overall riskiness of marijuana use, and 3) variable state laws or practice policies. CONCLUSIONS: Experts disagree and are uncertain about the importance of opioid tapering for patients with marijuana use. Experts were influenced by patient factors, provider beliefs, and marijuana policy, highlighting the need for further research.

Stern, C., C. de Carvalho, et al. (2017). "Effects of cannabinoid drugs on aversive or rewarding drug-associated memory extinction and reconsolidation." Neuroscience **in press**.

Posttraumatic stress and drug use disorders may stem from aberrant memory formation. As the endocannabinoid (eCB) system has a pivotal role in emotional memory processing and related synaptic plasticity, here we seek to review and discuss accumulating evidence on how and where in the brain interventions targeting the eCB system would attenuate outcomes associated with traumatic events and/or drug addiction through memory extinction facilitation or reconsolidation disruption. Currently available data from mouse, rat, monkey and healthy human studies investigating the effects of cannabinoid drugs on extinction and reconsolidation of aversive memories are more consistent than those related to rewarding drug-associated memories. Interventions able to attenuate aversive memories by extinction facilitation or reconsolidation disruption have boosted the anandamide-induced activation of cannabinoid type-1 (CB1) receptors. A still limited number of studies report that CB1 receptor activation could also be effective in facilitating the extinction or disrupting the reconsolidation of rewarding drug-associated memories. The reinstatement of extinguished drug memories (relapse) is reduced by CB1 receptor antagonism. The cannabidiol has shown to be effective in any of the aforementioned cases, albeit its mechanism of action is not fully understood. Brain areas in which cannabinoid drugs induce these effects include the prefrontal cortex, amygdala, hippocampus, and/or nucleus accumbens. The potential role of 2-arachidonoylglycerol (2-AG) and cannabinoid type-2 (CB2) receptors in emotional memory extinction and reconsolidation is currently under investigation. Overall, preclinical data support a closer look into certain cannabinoid drugs owing to their safety and potential therapeutic value against stress-related and drug use disorders.

Stetten, N., J. Pomeranz, et al. (2020). "The level of evidence of medical marijuana use for treating disabilities: a scoping review." Disabil Rehabil **42**(9): 1190-1201.

Purpose: Twenty-nine states have bypassed federal regulations by legalizing marijuana (MJ) either medicinally, recreationally or both. The FDA states that there is no empirical evidence that MJ is effective to treat these disorders. With over a billion individuals living with a disability across the globe, it is crucial to fully research the efficaciousness and safety of medical MJ to treat this population. The purpose to present the results of a scoping review of studies focused on the levels of evidence currently available on medical MJ's efficacy in treatment across a large range of disabilities.Methods: Databases were searched for research articles on the current level of evidence to support medical MJ use among people with disabilities.Results: Forty-one peer reviewed articles met the inclusion criteria. Articles focused on attention deficit hyperactivity disorder, post-traumatic stress disorder, depression, schizophrenia, spinal cord injury, multiple sclerosis/movement disorders, fibromyalgia, epilepsy, with some that focused on multiple disabilities.Conclusions: The level of evidence for the use of medical MJ among people with disabilities varies greatly, and has a clear lack of methodologically sound studies. Overall, medical MJ does not improve the level of functioning, but it may improve the overall quality of life for people with disabilities.Implications for RehabilitationEpilepsy can be a disabling chronic disorder which not only impacts physically but can restricts quality of life.Quality of life is diminished even more with treatment resistant epilepsy.Chronic pain is the leading cause of disability and is the most common cause of long-term disability.There is sufficient evidence that medical marijuana is effective in treating epileptic seizures and chronic pain.Medical marijuana may improve the level of functioning and quality of life for individuals with certain disabilities.

Stith, S. S., J. P. Diviant, et al. (2020). "Alleviative effects of Cannabis flower on migraine and headache." Journal of Integrative Medicine.

Objective Few studies to date have measured the real-time effects of consumption of common and commercially available Cannabis products for the treatment of headache and migraine under naturalistic conditions. This study examines, for the first time, the effectiveness of using dried Cannabis flower, the most widely used type of Cannabis product in the United States, in actual time for treatment of headache- and migraine-related pain and the associations between different product characteristics and changes in symptom intensity following Cannabis use. Methods Between 06/10/2016 and 02/12/2019, 699 people used the Releaf Application to record real-time details of their Cannabis use, including product characteristics and symptom intensity levels prior to and following self-administration; data included 1910 session-level attempts to treat headache- (1328 sessions) or migraine-related pain (582 sessions). Changes in headache- or migraine-related pain intensity were measured on a 0−10 scale prior to, and immediately, following Cannabis consumption. Results Ninety-four percent of users experienced symptom relief within a two-hour observation window. The average symptom intensity reduction was 3.3 points on a 0−10 scale (standard deviation = 2.28, Cohen’s d = 1.58), with males experiencing greater relief than females (P < 0.001) and a trend that younger users (< 35 years) experience greater relief than older users (P = 0.08). Mixed effects regression models showed that, among the known (i.e., labeled) product characteristics, tetrahydrocannabinol levels 10% and higher are the strongest independent predictors of symptom relief, and this effect is particularly prominent in headache rather than migraine sufferers (P < 0.05), females (P < 0.05) and younger users (P < 0.001). Females and younger users also appear to gain greater symptom relief from flower labeled as “C. indica” rather than “C. sativa” or other hybrid strains. Conclusion These results suggest that whole dried Cannabis flower may be an effective medication for treatment of migraine- and headache-related pain, but the effectiveness differs according to characteristics of the Cannabis plant, the combustion methods, and the age and gender of the patient.

Stith, S. S., J. M. Vigil, et al. (2018). "Patient-Reported Symptom Relief Following Medical Cannabis Consumption." Front Pharmacol **9**: 916.

Background: The Releaf App(TM) mobile software application (app) data was used to measure self-reported effectiveness and side effects of medical cannabis used under naturalistic conditions. Methods: Between 5/03/2016 and 12/16/2017, 2,830 Releaf App(TM) users completed 13,638 individual sessions self-administering medical cannabis and indicated their primary health symptom severity rating on an 11-point (0-10) visual analog scale in real-time prior to and following cannabis consumption, along with experienced side effects. Results: Releaf App(TM) responders used cannabis to treat myriad health symptoms, the most frequent relating to pain, anxiety, and depressive conditions. Significant symptom severity reductions were reported for all the symptom categories, with mean reductions between 2.8 and 4.6 points (ds ranged from 1.29-2.39, ps < 0.001). On average, higher pre-dosing symptom levels were associated with greater reported symptom relief, and users treating anxiety or depression-related symptoms reported significantly more relief (ps < 0.001) than users with pain symptoms. Of the 42 possible side effects, users were more likely to indicate and showed a stronger correlation between symptom relief and experiences of positive (94% of sessions) or a context-specific side effects (76%), whereas negative side effects (60%) were associated with lessened, yet still significant symptom relief and were more common among patients treating a depressive symptom relative to patients treating anxiety and pain-related conditions. Conclusion: Patient-managed cannabis use is associated with clinically significant improvements in self-reported symptom relief for treating a wide range of health conditions, along with frequent positive and negative side effects.

Stockings, E., G. Campbell, et al. (2018). "Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies." Pain.

This review examines evidence cannabinoids in chronic non-cancer pain (CNCP), and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 RCTs and 57 observational studies. Forty-eight studies examined neuropathic pain, seven studies examined fibromyalgia, one rheumatoid arthritis, and 48 other CNCP (13 MS-related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, PERs for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo), significant effect for cannabinoids, number needed to treat to benefit (NNTB): 24 (95%CI 15-61); for 50% reduction in pain, PERs were 18.2% vs. 14.4%; no significant difference. Pooled change in pain intensity (standardised mean difference: -0.14, 95%CI -0.20, -0.08) was equivalent to 3mm on a 100mm visual analogue scale greater than placebo. In RCTs, PERs for all-cause AEs were 81.2% vs. 66.2%; number needed to treat to harm (NNTH): 6 (95%CI 5-8). There were no significant impacts upon physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest NNTB are high, and NNTH low, with limited impact on other domains. It appears unlikely that cannabinoids are highly effective medicines for CNCP.

Stockings, E., D. Zagic, et al. (2018). "Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence." Journal of Neurology, Neurosurgery &amp;amp; Psychiatry.

Review evidence for cannabinoids as adjunctive treatments for treatment-resistant epilepsy. Systematic search of Medline, Embase and PsycINFO was conducted in October 2017. Outcomes were: 50%+ seizure reduction, complete seizure freedom; improved quality of life (QoL). Tolerability/safety were assessed by study withdrawals, adverse events (AEs) and serious adverse events (SAEs). Analyses were conducted in Stata V.15.0. 36 studies were identified: 6 randomised controlled trials (RCTs), 30 observational studies. Mean age of participants was 16.1 years (range 0.5–55 years). Cannabidiol (CBD) 20 mg/kg/day was more effective than placebo at reducing seizure frequency by 50%+(relative risk (RR) 1.74, 95% CI 1.24 to 2.43, 2 RCTs, 291 patients, low Grades of Recommendation, Assessment, Development and Evaluation (GRADE) rating). The number needed to treat for one person using CBD to experience 50%+ seizure reduction was 8 (95% CI 6 to 17). CBD was more effective than placebo at achieving complete seizure freedom (RR 6.17, 95% CI 1.50 to 25.32, 3 RCTs, 306 patients, low GRADE rating), and improving QoL (RR 1.73, 95% CI 1.33 to 2.26), however increased risk of AEs (RR 1.24, 95% CI 1.13 to 1.36) and SAEs (RR 2.55, 95% CI 1.48 to 4.38). Pooled across 17 observational studies, 48.5% (95% CI 39.0% to 58.1%) of patients reported 50%+ reductions in seizures; in 14 observational studies 8.5% (95% CI 3.8% to 14.5%) were seizure-free. Twelve observational studies reported improved QoL (55.8%, 95% CI 40.5 to 70.6); 50.6% (95% CI 31.7 to 69.4) AEs and 2.2% (95% CI 0 to 7.9) SAEs. Pharmaceutical-grade CBD as adjuvant treatment in paediatric-onset drug-resistant epilepsy may reduce seizure frequency. Existing RCT evidence is mostly in paediatric samples with rare and severe epilepsy syndromes; RCTs examining other syndromes and cannabinoids are needed.PROSPERO registration number CRD42017055412.

Suhre, W., V. O’Reilly-Shah, et al. (2020). "Cannabis use is associated with a small increase in the risk of postoperative nausea and vomiting: a retrospective machine-learning causal analysis." BMC Anesthesiology **20**(1): 115.

Cannabis legalization may contribute to an increased frequency of chronic use among patients presenting for surgery. At present, it is unknown whether chronic cannabis use modifies the risk of postoperative nausea and vomiting (PONV).

Sundaramurthi, H., A. Moran, et al. (2019). Emerging Drug Therapies for Inherited Retinal Dystrophies. Retinal Degenerative Diseases, Cham, Springer International Publishing.

Worldwide, 1 in 2000 people suffer from inherited retinal dystrophies (IRD). Individuals with IRD typically present with progressive vision loss that ultimately results in blindness. Unfortunately, effective treatment options are not widely available due to the genetic and clinical heterogeneity of these diseases. There are multiple gene, cell, and drug-based therapies in various phases of clinical trials for IRD. This mini-review documents current progress made in drug-based clinical trials for treating IRD.

Suraev, A., R. R. Grunstein, et al. (2020). "Cannabidiol (CBD) and Δ(9)-tetrahydrocannabinol (THC) for chronic insomnia disorder ('CANSLEEP' trial): protocol for a randomised, placebo-controlled, double-blinded, proof-of-concept trial." BMJ Open **10**(5): e034421.

INTRODUCTION: Insomnia is a highly prevalent and costly condition that is associated with increased health risks and healthcare utilisation. Anecdotally, cannabis use is frequently reported by consumers to promote sleep. However, there is limited research on the effects of cannabis on sleep and daytime function in people with insomnia disorder using objective measures. This proof-of-concept study will evaluate the effects of a single dose of an oral cannabis-based medicine on sleep and daytime function in participants with chronic insomnia disorder. METHODS AND ANALYSIS: A randomised, crossover, placebo-controlled, single-dose study design will be used to test the safety and efficacy of an oral oil solution ('ETC120') containing 10 mg Δ(9)-tetrahydrocannabinol (THC) and 200 mg cannabidiol (CBD) in 20 participants diagnosed with chronic insomnia disorder. Participants aged 35-60 years will be recruited over an 18-month period commencing August 2019. Each participant will receive both the active drug and matched placebo, in a counterbalanced order, during two overnight study assessment visits, with at least a 1-week washout period between each visit. The primary outcomes are total sleep time and wake after sleep onset assessed via polysomnography. In addition, 256-channel high-density electroencephalography and source modelling using structural brain MRI will be used to comprehensively examine brain activation during sleep and wake periods on ETC120 versus placebo. Next-day cognitive function, alertness and simulated driving performance will also be investigated. ETHICS AND DISSEMINATION: Ethics approval was received from Bellberry Human Research Ethics Committee (2018-04-284). The findings will be disseminated in a peer-reviewed open-access journal and at academic conferences. TRIAL REGISTRATION NUMBER: ANZCTRN12619000714189.

Szaflarski, M., P. McGoldrick, et al. (2020). "Attitudes and knowledge about cannabis and cannabis-based therapies among US neurologists, nurses, and pharmacists." Epilepsy Behav **109**: 107102.

Use of cannabinoid therapies is on the rise in the United States, but responses of healthcare professionals and their knowledge of these therapies have been mixed. More information is needed about factors associated with healthcare professionals' attitudes and knowledge about medical cannabis. We conducted an online survey of US-based neurologists, nurse practitioners (NPs)/nurses, and pharmacists in August-September of 2018 (n = 451). We constructed perceived knowledge and attitudes scales and a knowledge index from multiple items and assessed state cannabis laws, participant's sociodemographics, workplace type and policies, and patient population. We used ordinary least-squares regression to examine associations among study variables. Over 80% of participants supported use and legalization of medical cannabis, especially cannabidiol (CBD) for epilepsy and when prescribed by a medical provider, but 40-50% (depending on item) felt unfamiliar with cannabinoid pharmacology and clinical applications. A total of 43% favored legal recreational cannabis. Pharmacists scored higher on the knowledge test than neurologists and NPs/nurses, but NPs/nurses had more favorable attitudes than neurologists and higher perceived knowledge than pharmacists. Both knowledge indicators predicted attitudes. State cannabis access and favorable workplace policies were associated with higher knowledge and more favorable attitudes. Healthcare professionals see potential in cannabis therapies but report significant knowledge gaps. Professional cannabinoid education is needed to address growing patient and provider demand for knowledge about cannabinoid therapies.

Szigethy, E. (2018). "Pain Management in Patients With Inflammatory Bowel Disease." Gastroenterology & Hepatology **14**(1): 53-56.

Abdominal pain is a common symptom in patients with inflammatory bowel disease (IBD) and has a profound negative impact on patients’ lives. There are growing data suggesting that pain is variably related to the degree of active inflammation. Given the multifactorial etiologies underlying the pain, the treatment of abdominal pain in the IBD population is best accomplished by individualized plans. This review covers four clinically relevant categories of abdominal pain in patients with IBD, namely, inflammation, surgical complications, bacterial overgrowth, and neurobiological processes and how pain management can be addressed in each of these cases. The role of genetic factors, psychological factors, and psychosocial stress in pain perception and treatment will also be addressed. Lastly, psychosocial, pharmacological, and procedural pain management techniques will be discussed. An extensive review of the existing literature reveals a paucity of data regarding pain management specific to IBD. In addition, there is growing consensus suggesting a spectrum between IBD and irritable bowel syndrome (IBS) symptoms. Thus, this review for adult and pediatric clinicians also incorporates the literature for the treatment of functional abdominal pain and the clinical consensus from IBD and IBS experts on pharmacological, behavioral, and procedural methods to treat abdominal pain in this population.

Sznitman, S. R., L. Pinsky-Talbi, et al. (2020). "Cannabis and synthetic cannabinoid exposure reported to the Israel poison information center: Examining differences in exposures to medical and recreational compounds." International Journal of Drug Policy **77**: 102711.

Background Increasing use of cannabis for medical and recreational purposes has augmented concerns about associated poisoning, and specifically pediatric and adolescent poisonings. Synthetic cannabinoids, often marketed as cannabis replacement, have recently emerged and knowledge and awareness of their toxic effects is growing. The objective of this study was to characterize and compare cannabinoid poisonings (medical and recreational cannabis, and synthetic cannabinoids) in Israel during the period 2007–2018. Methods The three types of cannabinoid exposures reported to the Israel Poison Information Center (IPIC) between 2007 and 2018 were identified. Differences in distribution of the three types of agents with respect to demographic and clinical factors were examined using univariate statistics, and time trends were plotted. Results Out of the total 615 poison-exposure cases identified, 55% were recreational cannabis cases, 33% were synthetic cannabinoid cases and 12% were medical cannabis cases. Compared to recreational cannabis exposures, synthetic cannabinoid exposures were more likely to be male, to have both gastrointestinal and cardiovascular manifestations and less likely to be called in by the public as opposed to called in by health care professionals and less likely to be treated on-site. Medical cannabis exposures were less likely to be male, more likely to be called in by the public, less likely to present with co-use of other substances and more likely to have gastrointestinal manifestations. Throughout the study period an increase in exposure cases were observed for medical and recreational cannabis cases, whereas synthetic cannabinoid cases showed an increase until 2014 and then a steep decrease. Conclusions Despite the low toxicity of different types of cannabinoids, training of physicians and other health care professionals related to cannabinoid poisoning is important. This is particularly important in jurisdictions where legal access to cannabis is becoming increasingly available.

Sznitman, S. R., S. Vulfsons, et al. (2020). "Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study." BMJ Supportive &amp; Palliative Care: bmjspcare-2019-001938.

Objectives Medical cannabis (MC) is increasingly being used for treatment of chronic pain symptoms. Among patients there is also a growing preference for the use of MC to manage sleep problems. The aim of the current study was to examine the associations between use of whole plant cannabis and sleep problems among chronic pain patients.Methods A total of 128 individuals with chronic pain over the age of 50 years were recruited from the Rambam Institute for Pain Medicine in Haifa, Israel. Of them, 66 were MC users and 62 were non-users. Regression models tested the differences in sleep problems between the two groups. Furthermore, Pearson correlations between MC use measures (dose, length and frequency of use, number of strains used, tetrahydrocannabinol/cannabidiol levels) and sleep problems were assessed among MC users.Results After adjustment for age, sex, pain level and use of sleep and anti-depressant medications, MC use was associated with less problems with waking up at night compared with non-MC use. No group differences were found for problems with falling asleep or waking up early without managing to fall back asleep. Frequent MC use was associated with more problems waking up at night and falling asleep.Conclusions MC use may have an overall positive effect on maintaining sleep throughout the night in chronic pain patients. At the same time, tolerance towards potential sleep-inducing properties of MC may occur with frequent use. More research based on randomised control trials and other longitudinal designs is warranted.

Takakuwa, K. M. (2020). "A history of the Society of Cannabis Clinicians and its contributions and impact on the US medical cannabis movement." Int J Drug Policy **79**: 102749.

The US medical marijuana movement has come about in a relatively short period of time. Despite millennia in which cannabis was used medically, it was taxed and then banned in the US during the 20th century. It would take a number of factors working concurrently-increasing social use, scientific developments, the AIDS epidemic, and political activism-before its use became accepted again. Some of the groundwork for the medical marijuana movement to take hold was laid out by cannabis clinicians, practitioners who recognized the medical potential of the plant and its constituent compounds, kept abreast of the relevant scientific discoveries, and risked their medical licenses, professional reputations and even arrest to approve and guide medical use to their patients as it became legal in their states. Once the tide started moving, it did so relatively quickly. In this article, a history detailing the first and oldest U.S. medical organization promoting the use of medical cannabis and its founder is reviewed, shedding light on an aspect of history within the medical cannabis movement that is largely unrecognized.

Takeda, S., E. Ikeda, et al. (2017). Chapter 74 - Effects of Δ9-Tetrahydrocannabinol in Human Breast Cancer A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 722-728.

Abstract Although Δ9-tetrahydrocannabinol (Δ9-THC), a major cannabinoid produced by Cannabis sativa (marijuana), is generally considered to induce antitumor effects in a wide variety of cancers, this cannabinoid has also been shown to stimulate the proliferation of cancer cells under certain conditions both in vitro and in vivo. Δ9-THC is now being used medicinally (ie, dronabinol, a synthetic form of Δ9-THC) as well as recreationally (drug abuse); however, Δ9-THC is not currently used as an anticancer agent in patients. In this chapter, we will summarize the biological effects of Δ9-THC on breast cancer cells, and provide an insight into the possible mechanisms responsible for modulating Δ9-THC sensitivity to breast cancer cells.

Tellioğlu, T. and Z. Tellioğlu (2017). Chapter 90 - The Use of Medical Marijuana in the Treatment of Psychiatric Disorders A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 869-876.

Abstract In this chapter, we aimed to investigate the current evidence in the medical literature about the possible use of medical marijuana in the treatment of psychiatric disorders. Medical marijuana refers simply to the use of marijuana or cannabis derivates as a medical therapy to treat a medical condition or to relieve its symptoms. Marijuana is often consumed recreationally for its effects of heightened mood (euphoria), and relaxation, however, historic evidence shows that it was also used as a medicine. While medicinal use of marijuana has been debated for the treatment of medical conditions, (ie, pain, multiple sclerosis, nausea in cancer chemotherapy), patients who are suffering from mental disorders have also reported some benefit. Although it appears like majority of anecdotally reported improvements are related to the effects of heightened mood or euphoria, and relaxation, there is some meaningful and promising research data available for some anxiety disorders; especially posttraumatic stress disorder (PTSD). Medicine, as an evidence-based science, has been approaching the medical marijuana issue very cautiously due to the lack of sufficient, supportive clinical data, and also due to the legal risk of being penalized by using, researching or recommending a chemical compound which has been declared as a crime under federal law.

Temple, L. M. and J. B. Leikin (2020). "Tetrahydrocannabinol - friend or foe? - Debate." Clin Toxicol (Phila) **58**(2): 75-81.

Background: Tetrahydrocannabinol (THC) is a psychoactive cannabinoid that has been used to treat various conditions. However, due to various adverse effects, its widespread promotion and use has been controversial. It is this aspect (encouraged by various state legislatures) that forms the basis for an edited debate between an Integrative Family Medicine physician and a Medical Toxicologist.Methods: Pro/Con debate with literature review and commentary.Discussion: Medical THC is beneficial for various conditions (especially pain relief). However the dosing, titration and delivery system has of yet to be precisely defined. There is a paucity of studies focusing on cannabidiol (CBD) efficacy without THC, which further complicates medical cannabis clinical studies. Cannabis toxicity tends to be cumulative, which makes it more difficult to identify at the bedside.Conclusion: There is conflicting data regarding the efficacy and toxicity of medical use of THC.

Thiele, E. A., E. D. Marsh, et al. (2018). "Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial." The Lancet **391**(10125): 1085-1096.

Summary Background Patients with Lennox-Gastaut syndrome, a rare, severe form of epileptic encephalopathy, are frequently treatment resistant to available medications. No controlled studies have investigated the use of cannabidiol for patients with seizures associated with Lennox-Gastaut syndrome. We therefore assessed the efficacy and safety of cannabidiol as an add-on anticonvulsant therapy in this population of patients. Methods In this randomised, double-blind, placebo-controlled trial done at 24 clinical sites in the USA, the Netherlands, and Poland, we investigated the efficacy of cannabidiol as add-on therapy for drop seizures in patients with treatment-resistant Lennox-Gastaut syndrome. Eligible patients (aged 2–55 years) had Lennox-Gastaut syndrome, including a history of slow (<3 Hz) spike-and-wave patterns on electroencephalogram, evidence of more than one type of generalised seizure for at least 6 months, at least two drop seizures per week during the 4-week baseline period, and had not responded to treatment with at least two antiepileptic drugs. Patients were randomly assigned (1:1) using an interactive voice response system, stratified by age group, to receive 20 mg/kg oral cannabidiol daily or matched placebo for 14 weeks. All patients, caregivers, investigators, and individuals assessing data were masked to group assignment. The primary endpoint was percentage change from baseline in monthly frequency of drop seizures during the treatment period, analysed in all patients who received at least one dose of study drug and had post-baseline efficacy data. All randomly assigned patients were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02224690. Findings Between April 28, 2015, and Oct 15, 2015, we randomly assigned 171 patients to receive cannabidiol (n=86) or placebo (n=85). 14 patients in the cannabidiol group and one in the placebo group discontinued study treatment; all randomly assigned patients received at least one dose of study treatment and had post-baseline efficacy data. The median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannibidiol group and 21·8% (IQR −45·7 to 1·7) in the placebo group. The estimated median difference between the treatment groups was −17·21 (95% CI −30·32 to −4·09; p=0·0135) during the 14-week treatment period. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate. The most common adverse events were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. 12 (14%) patients in the cannabidiol group and one (1%) patient in the placebo group withdrew from the study because of adverse events. One patient (1%) died in the cannabidiol group, but this was considered unrelated to treatment. Interpretation Add-on cannabidiol is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated. The long-term efficacy and safety of cannabidiol is currently being assessed in the open-label extension of this trial.

Thomas R. Arkell, Nicholas Lintzeris, et al. (2019). "Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition." Psychopharmacology.

Background: The main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), can impair driving performance. Cannabidiol (CBD), a non-intoxicating cannabis component, is thought to mitigate certain adverse effects of THC. It is possible then that cannabis containing equivalent CBD and THC will differentially affect driving and cognition relative to THC-dominant cannabis.

Aims : The present study investigated and compared the effects of THC-dominant and THC/CBD equivalent cannabis on simulated driving and cognitive performance.

Methods: In a randomized, double-blind, within-subjects crossover design, healthy volunteers (n = 14) with a history of light cannabis use attended three outpatient experimental test sessions in which simulated driving and cognitive performance were assessed at two timepoints (20–60 min and 200–240 min) following vaporization of 125 mg THC-dominant (11% THC; < 1% CBD), THC/CBD equivalent (11% THC, 11% CBD), or placebo (< 1% THC/CBD) cannabis.

Results/outcomes: Both active cannabis types increased lane weaving during a car-following task but had little effect on other driving performance measures. Active cannabis types impaired performance on the Digit Symbol Substitution Task (DSST), Divided Attention Task (DAT) and Paced Auditory Serial Addition Task (PASAT) with impairment on the latter two tasks worse with THC/CBD equivalent cannabis. Subjective drug effects (e.g., “stoned”) and confidence in driving ability did not vary with CBD content. Peak plasma THC concentrations were higher following THC/CBD equivalent cannabis relative to THC-dominant cannabis, suggesting a possible pharmacokinetic interaction.

Conclusions/interpretation: Cannabis containing equivalent concentrations of CBD and THC appears no less impairing than THC-dominant cannabis, and in some circumstances, CBD may actually exacerbate THC-induced impairment.

Tomko, A. M., E. G. Whynot, et al. (2020). "Anti-Cancer Potential of Cannabinoids, Terpenes, and Flavonoids Present in Cannabis." Cancers **12**(7): 1985.

In recent years, and even more since its legalization in several jurisdictions, cannabis and the endocannabinoid system have received an increasing amount of interest related to their potential exploitation in clinical settings. Cannabinoids have been suggested and shown to be effective in the treatment of various conditions. In cancer, the endocannabinoid system is altered in numerous types of tumours and can relate to cancer prognosis and disease outcome. Additionally, cannabinoids display anticancer effects in several models by suppressing the proliferation, migration and/or invasion of cancer cells, as well as tumour angiogenesis. However, the therapeutic use of cannabinoids is currently limited to the treatment of symptoms and pain associated with chemotherapy, while their potential use as cytotoxic drugs in chemotherapy still requires validation in patients. Along with cannabinoids, cannabis contains several other compounds that have also been shown to exert anti-tumorigenic actions. The potential anti-cancer effects of cannabinoids, terpenes and flavonoids, present in cannabis, are explored in this literature review.

Torres, C. A., C. Medina-Kirchner, et al. (2020). "Totality of the Evidence Suggests Prenatal Cannabis Exposure Does Not Lead to Cognitive Impairments: A Systematic and Critical Review." Frontiers in Psychology **11**: 816.

Background: Despite limited data demonstrating pronounced negative effects of prenatal cannabis exposure, popular opinion and public policies still reflect the belief that cannabis is fetotoxic. Methods: This article provides a critical review of results from longitudinal studies examining the impact of prenatal cannabis exposure on multiple domains of cognitive functioning in individuals aged 0 to 22 years. A literature search was conducted through PsycINFO, PubMed, and Google Scholar. Articles were included if they examined the cognitive performance of offspring exposed to cannabis in utero. Results: An examination of the total number of statistical comparisons (n = 1,001) between groups of participants that were exposed to cannabis prenatally and non-exposed controls revealed that those exposed performed differently on a minority of cognitive outcomes (worse on <3.5 percent and better in <1 percent). The clinical significance of these findings appears to be limited because cognitive performance scores of cannabis-exposed groups overwhelmingly fell within the normal range when compared against normative data adjusted for age and education. Conclusions: The current evidence does not suggest that prenatal cannabis exposure alone is associated with clinically significant cognitive functioning impairments.

Tran, T. and R. Kavuluru (2020). "Social media surveillance for perceived therapeutic effects of cannabidiol (CBD) products." International Journal of Drug Policy **77**: 102688.

Background CBD products have risen in popularity given CBD's therapeutic potential and lack of legal oversight, despite lacking conclusive scientific evidence for widespread over-the-counter usage for many of its perceived benefits. While medical evidence is being generated, social media surveillance offers a fast and inexpensive alternative to traditional surveys in ascertaining perceived therapeutic purposes and modes of consumption for CBD products. Methods We collected all comments from the CBD subreddit posted between January 1 and April 30, 2019 as well as comments submitted to the FDA regarding regulation of cannabis-derived products and analyzed them using a rule-based language processing method. A relative ranking of popular therapeutic uses and product groups for CBD is obtained based on frequency of pattern matches including precise queries that entail identifying mentions of the condition, a CBD product, and some “trigger” phrase indicating therapeutic use. We validated the social media-based findings using a similar analysis on comments to the U.S. Food and Drug Administration's (FDA) 2019 request-for-comments on cannabis-derived products. Results CBD is mostly discussed as a remedy for anxiety disorders and pain and this is consistent across both comment sources. Of comments posted to the CBD subreddit during the monitored time span, 6.19% mentioned anxiety at least once with at least 6.02% of these comments specifically mentioning CBD as a treatment for anxiety (i.e., 0.37% of total comments). The most popular CBD product group is oil and tinctures. Conclusion Social media surveillance of CBD usage has the potential to surface new therapeutic use-cases as they are posted. Contemporary social media data indicate, for example, that stress and nausea are frequently mentioned as therapeutic use cases for CBD without corresponding evidence, that affirms or denies, in the research literature. However, the abundance of anecdotal claims warrants serious scientific exploration moving forward. Meanwhile, as FDA ponders regulation, our effort demonstrates that social data offers a convenient affordance to surveil for CBD usage patterns in a way that is fast and inexpensive and can inform conventional electronic surveys.

Tschoe, C., L. Johnson, et al. (2020). "Serotonin Syndrome with Exposure from Tetrahydrocannabinol: a Case Report to Highlight the Side Effects of Increasing Use of CBD Products (5302)." Neurology **94**(15 Supplement): 5302.

Objective: N/ABackground: Serotonin syndrome is a potentially life-threatening condition caused by over-activation of the serotonin (5-HT) system in the CNS. This can occur with the therapeutic use of serotonergic agents or inadvertent complex drug interactions between serotonergic agents. Clinical presentation varies widely in severity and is diagnosed by the decision rules of Hunter Serotonin Toxicity Criteria, utilizing the three main clinical categories: altered mental status, autonomic hyperactivity, and neuromuscular abnormalities.Design/Methods: A 63 year-old male with medical history most notable for restless leg syndrome (on ropinirole), chronic lymphocytic leukemia, depression on duloxetine, and chronic alcohol abuse presented with altered mental status, shaking, diaphoresis, and an inability to walk. He had initiated intake of THC-infused cheese as a neuropathic pain control measure. On examination, he was afebrile, hypertensive and mildly tachycardic, somnolent, diaphoretic, and diffusely hyperreflexic. Urine toxicology screen was positive for tetrahydrocannabinol (THC). He was treated with intravenous fluids and lorazepam with improvement of symptoms. With continued supportive therapy and discontinuation of duloxetine, the patient completely recovered within 48 hours and was discharged home without residual symptoms.Results: N/AConclusions: The cannabinoid (CB) receptors and endogenous agonists are widely distributed throughout the CNS and are involved in the regulation of mood. This endocannabinoid system is known to regulate serotonergic system through several mechanisms: modulation of 5-HT release, receptor expression, and regulation of excitability of 5-HT neurons.With the legalization of marijuana and increasing access to cannabinoid-containing products, it is imperative to raise awareness of the serotonergic effects of these products and to educate patients to avoid use of these products if they are currently taking a serotonergic agent. Complete workup of a patient with serotonin syndrome should include a urine drug screen and comprehensive social history.Disclosure: Dr. Tschoe has nothing to disclose. Dr. Johnson has nothing to disclose. Dr. Giugliano has nothing to disclose. Dr. Sarwal has nothing to disclose.

Turna, J., S. K. Syan, et al. (2019). "Cannabidiol as a Novel Candidate Alcohol Use Disorder Pharmacotherapy: A Systematic Review." Alcohol Clin Exp Res 43(4): 550-563.

There is substantial interest in the therapeutic potential of cannabidiol (CBD), a nonpsychoactive cannabinoid found in plants of the genus Cannabis. The goal of the current systematic review was to characterize the existing literature on this topic and to evaluate the credibility of CBD as a candidate pharmacotherapy for alcohol use disorder (AUD). Using a comprehensive search strategy, 303 unique potential articles were identified and 12 ultimately met criteria for inclusion (8 using rodent models, 3 using healthy adult volunteers, and 1 using cell culture). In both rodent and cell culture models, CBD was found to exert a neuroprotective effect against adverse alcohol consequences on the hippocampus. In rodent models, CBD was found to attenuate alcohol-induced hepatotoxicity, specifically, alcohol-induced steatosis. Finally, findings from preclinical rodent models also indicate that CBD attenuates cue-elicited and stress-elicited alcohol seeking, alcohol self-administration, withdrawal-induced convulsions, and impulsive discounting of delayed rewards. In human studies, CBD was well tolerated and did not interact with the subjective effects of alcohol. Collectively, given its favorable effects on alcohol-related harms and addiction phenotypes in preclinical models, CBD appears to have promise as a candidate AUD pharmacotherapy. This is further bolstered by the absence of abuse liability and its general tolerability. A clear limitation to the literature is the paucity of human investigations. Human preclinical and clinical studies are needed to determine whether these positive effects in model systems substantively translate into clinically relevant outcomes.

Turna, J., B. Patterson, et al. (2017). "Is cannabis treatment for anxiety, mood, and related disorders ready for prime time?" Depression and Anxiety **34**(11): 1006-1017.

Anxiety and related disorders are the most common mental conditions affecting the North American population. Despite their established efficacy, first-line antidepressant treatments are associated with significant side effects, leading many afflicted individuals to seek alternative treatments. Cannabis is commonly viewed as a natural alternative for a variety of medical and mental health conditions. Currently, anxiety ranks among the top five medical symptoms for which North Americans report using medical marijuana. However, upon careful review of the extant treatment literature, the anxiolytic effects of cannabis in clinical populations are surprisingly not well-documented. The effects of cannabis on anxiety and mood symptoms have been examined in healthy populations and in several small studies of synthetic cannabinoid agents but there are currently no studies which have examined the effects of the cannabis plant on anxiety and related disorders. In light of the rapidly shifting landscape regarding the legalization of cannabis for medical and recreational purposes, it is important to highlight the significant disconnect between the scientific literature, public opinion, and related policies. The aim of this article is to provide a comprehensive review of the current cannabis treatment literature, and to identify the potential for cannabis to be used as a therapeutic intervention for anxiety, mood, and related disorders. Searches of five electronic databases were conducted (PubMed, MEDLINE, Web of Science, PsychINFO, and Google Scholar), with the most recent in February 2017. The effects of cannabis on healthy populations and clinical psychiatric samples will be discussed, focusing primarily on anxiety and mood disorders.

Unal, E., B. Anderson, et al. (2019). "Cannabinoids: A Guide for Use in the World of Gastrointestinal Disease." *Journal of Clinical Gastroenterology Publish Ahead of Print*.

Cannabinoids have been known as the primary component of cannabis for decades, but the characterization of the endocannabinoid system (ECS) in the 1990s opened the doors for cannabis’ use in modern medicine. The 2 main receptors of this system, cannabinoid receptors 1 and 2, are found on cells of various tissues, with significant expression in the gastrointestinal (GI) tract. The characterization of the ECS also heralded the understanding of endocannabinoids, naturally occurring compounds synthesized in the human body. Via secondary signaling pathways acting on vagal nerves, nociceptors, and immune cells, cannabinoids have been shown to have both palliative and detrimental effects on the pathophysiology of GI disorders. Although research on the effects of both endogenous and exogenous cannabinoids has been slow due to the complicated legal history of cannabis, discoveries of cannabinoids’ treatment potential have been found in various fields of medicine, including the GI world. Medical cannabis has since been offered as a treatment for a myriad of conditions and malignancies, including cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, multiple sclerosis, chronic pain, nausea, posttraumatic stress disorder, amyotrophic lateral sclerosis, cachexia, glaucoma, and epilepsy. This article hopes to create an overview of current research on cannabinoids and the ECS, detail the potential advantages and pitfalls of their use in GI diseases, and explore possible future developments in this field. The authors declare that they have nothing to disclose. Address correspondence to: John H. Marks, MD, FACS, FASCRS, Marks Colorectal Surgical Associates, Lankenau Medical Center, Medical Science Building, Suite 375, 100 East Lancaster Avenue, Wynnewood, PA 19096 (e-mail: marksj@mlhs.org). Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Vacaflor, B. E., O. Beauchet, et al. (2020). "Mental Health and Cognition in Older Cannabis Users: a Review." Canadian geriatrics journal : CGJ **23**(3): 242-249.

BACKGROUND: The impact of cannabis use on mental health and cognition in older adults remains unclear. With the recent legalization of cannabis in Canada, physicians will need up-to-date information about the mental and cognitive effects of cannabis use in this specific population. METHOD: A narrative review was conducted to summarize the literature on mental health and cognitive effects of cannabis use in older adults using Medline (OvidSP). RESULTS: A total of 16 studies were identified, including nine cross-sectional studies on mental health comorbidities reported by older cannabis users. The self-reported prevalence of mental and substance use disorders is approximately two to three times higher in older adults who report past-year cannabis use, compared to older adults who report using more than one year ago or never using. The remaining seven clinical trials found that short-term, low-dose medical cannabis was generally well-tolerated in older adults without prior serious mental illness. However, mental/cognitive adverse effects were not systematically assessed. CONCLUSION: Although preliminary findings suggests that low-dose, short-term medical cannabis does not carry significant risk of serious mental health and cognitive adverse effects in older adults without prior psychiatric history, epidemiological studies find a correlation between past-year cannabis use and poor mental health outcomes in community-dwelling older adults. These findings may indicate that longer term cannabis use in this population is detrimental to their mental health, although a direct causal link has not been established. Larger, longitudinal studies on the safety of medical cannabis in older adults are needed.

Vadivelu, N., A. M. Kai, et al. (2018). "Medical Marijuana: Current Concepts, Pharmacological Actions of Cannabinoid Receptor Mediated Activation, and Societal Implications." Current Pain and Headache Reports **22**(1): 3.

The purpose of the following review is to summarize the history and current policies related to marijuana use and prevalence, basic and clinical science pharmacological literature regarding efficacy, subpopulations of concern, and varying policies regarding its use at present.

van de Donk, T., M. Niesters, et al. (2018). "An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia." Pain.

In this experimental randomized placebo-controlled 4-way crossover trial, we explored the analgesic effects of inhaled pharmaceutical-grade cannabis in twenty chronic pain patients with fibromyalgia. We tested four different cannabis varieties with exact knowledge on their [INCREMENT]-tetrahydrocannabinol (THC), and cannabidiol (CBD) content: Bedrocan(R) (22.4 mg THC, < 1 mg CBD), Bediol(R) (13.4 mg THC, 17.8 mg CBD), Bedrolite(R) (18.4 mg CBD, < 1 mg THC) and a placebo variety without any THC or CBD. Following a single vapor inhalation, THC and CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores and drug high were measured for 3 hours. None of the treatments had an effect greater than placebo on spontaneous or electrical pain responses, although more subjects receiving Bediol(R) displayed a 30% decrease in pain scores compared to placebo (90% vs. 55% of patients, p = 0.01), with spontaneous pain scores correlating with the magnitude of drug high (rho = -0.5, p < 0.001). Cannabis varieties containing THC caused a significant increase in pressure pain threshold relative to placebo (p < 0.01). CBD inhalation increased THC plasma concentrations but diminished THC-induced analgesic effects, indicative of a synergistic pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD. This experimental trial shows the complex behavior of inhaled cannabinoids in chronic pain patients with just small analgesic responses after a single inhalation. Further studies are needed to determine long-term treatment effects on spontaneous pain scores, THC-CBD interactions and the role of psychotropic symptoms on pain relief.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND) , where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Vaucher, J., B. J. Keating, et al. (2017). "Cannabis use and risk of schizophrenia: a Mendelian randomization study." Molecular Psychiatry **23**: 1287.\

Cannabis use is observationally associated with an increased risk of schizophrenia, but whether the relationship is causal is not known. Using a genetic approach, we took 10 independent genetic variants previously identified to associate with cannabis use in 32 330 individuals to determine the nature of the association between cannabis use and risk of schizophrenia. Genetic variants were employed as instruments to recapitulate a randomized controlled trial involving two groups (cannabis users vs nonusers) to estimate the causal effect of cannabis use on risk of schizophrenia in 34 241 cases and 45 604 controls from predominantly European descent. Genetically-derived estimates were compared with a meta-analysis of observational studies reporting ever use of cannabis and risk of schizophrenia or related disorders. Based on the genetic approach, use of cannabis was associated with increased risk of schizophrenia (odds ratio (OR) of schizophrenia for users vs nonusers of cannabis: 1.37; 95% confidence interval (CI), 1.09–1.67; P-value=0.007). The corresponding estimate from observational analysis was 1.43 (95% CI, 1.19–1.67; P-value for heterogeneity =0.76). The genetic markers did not show evidence of pleiotropic effects and accounting for tobacco exposure did not alter the association (OR of schizophrenia for users vs nonusers of cannabis, adjusted for ever vs never smoker: 1.41; 95% CI, 1.09–1.83). This adds to the substantial evidence base that has previously identified cannabis use to associate with increased risk of schizophrenia, by suggesting that the relationship is causal. Such robust evidence may inform public health messages about cannabis use, especially regarding its potential mental health consequences.

Venkatesan, T., D. J. Levinthal, et al. (2019). "Role of chronic cannabis use: Cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome." Neurogastroenterol Motil 31 Suppl 2: e13606.

Cannabis is commonly used in cyclic vomiting syndrome (CVS) due to its antiemetic and anxiolytic properties. Paradoxically, chronic cannabis use in the context of cyclic vomiting has led to the recognition of a putative new disorder called cannabinoid hyperemesis syndrome (CHS). Since its first description in 2004, numerous case series and case reports have emerged describing this phenomenon. Although not pathognomonic, a patient behavior called "compulsive hot water bathing" has been associated with CHS. There is considerable controversy about how CHS is defined. Most of the data remain heterogenous with limited follow-up, making it difficult to ascertain whether chronic cannabis use is causal, merely a clinical association with CVS, or unmasks or triggers symptoms in patients inherently predisposed to develop CVS. This article will discuss the role of cannabis in the regulation of nausea and vomiting, specifically focusing on both CVS and CHS, in order to address controversies in this context. To this objective, we have collated and analyzed published case series and case reports on CHS in order to determine the number of reported cases that meet current Rome IV criteria for CHS. We have also identified limitations in the existing diagnostic framework and propose revised criteria to diagnose CHS. Future research in this area should improve our understanding of the role of cannabis use in cyclic vomiting and help us better understand and manage this disorder.

Vigano, A., S. Aprikian, et al. (2020). "Safety and effectiveness of medical cannabis as a complementary option for supportive cancer care: Results from the Cannabis Pilot Project." Journal of Clinical Oncology **38**(15\_suppl): 12106-12106.

12106Background: Access to medical cannabis (MC) is a common request by patients and caregivers in supportive cancer care (SCC). However, healthcare professionals require more evidence on MC safety and effectiveness. Methods: The Cannabis Pilot Project (CPP) was implemented at the Cedars Cancer Centre of the McGill University Health Centre to evaluate MC as a complementary option for symptom control in SCC. Referral to the CPP was reserved for patients who were receiving SCC but had not obtained adequate symptom relief. An interdisciplinary team (physician, nurse and research coordinator) was established to systematically assess patients, prescribe and monitor MC treatments and record data on their safety and effectiveness. Patients were enrolled in the CPP between February 2018 and December 2019 and reassessed at intervals of one to six months. Results: Ninety-six cancer patients (mean age 60.0y (±13.9); 41 (42.7%) males) had at least one follow-up (FUP) and were included in the study. The main cancer types were breast (19.8%), lung (9.4%) and colorectal (9.4%). Adverse events (top three: drowsiness, low energy and nausea) were reported in 28% of patients, with 9% having to stop MC. Mean Brief Pain Inventory scores significantly improved between baseline, FUP-2 and FUP-3 for worst pain (5.4± SEM 0.3 vs 4.3±0.3 and 3.7±0.4) and average pain severity (4.2±0.2 vs 3.2±0.3 and 3.2±0.4). Anorexia improved (3.4±0.3 vs 2.2±0.4 and 1.7±0.4), as measured via the revised Edmonton Symptom Assessment System (ESAS-r). ESAS-r wellbeing improved significantly between baseline and FUP-1 (4.4±0.2 vs 3.7±0.2). Between baseline and each FUP, approximately a third of patients dropped their use of concurrent medications (including analgesics, antidepressants and anxiolytics), as measured by the Medication Quantification Scale. Conclusions: The CPP data support the safety and effectiveness of MC as a complementary option for improving pain control, appetite and quality of life in SCC.

Vigano, A., M. Canac-Marquis, et al. (2020). "The Quebec Cannabis Registry: a pharmacovigilance and effectiveness study on the use of medical cannabis in cancer patients." Journal of Clinical Oncology **38**: 12109-12109.

12109 Background: The Quebec Cannabis Registry (QCR) was launched in 2015 to allow physicians to prescribe medical cannabis (MC) in the province of Quebec, Canada. This study aimed to investigate the safety and effectiveness of MC in cancer patients using pharmacovigilance data prospectively collected for up to 24 months. Methods: Patients were enrolled in the QCR between May 2015 and October 2018 and followed every 3 months. Study outcomes included adverse events (AE), pain severity and interference (Brief-Pain Inventory), wellbeing (Revised-Edmonton Symptom Assessment Scale) and overall health scale (EQ5D5L) at baseline and at each follow-up (F-UP). Significance of changes over time were assessed using repeated-measures ANOVA. Results: Out of the 2991 patients enrolled in the QCR, 358 (12.8%) were cancer patients (mean age 57.7 (± 14.6); 171 (47.8%) males). The main cancer types were breast (16.2%), lung (11.7%), leukemia (11.5%) and colorectal (11.2%). MC was prescribed primarily for pain (72.1%), anxiety (4.7%), nausea (4.5%), anorexia (3.9%), and insomnia (3.1%). A total of 13 patients (3.6%) reported AE with only three being serious (one unrelated to MC: stroke; and two possibly related: diarrhea, from CBD oil overdose and pneumonia from smoking MC). Mean scores significantly (p < 0.05) improved between baseline and 3 months F-UP for pain severity (4.8 ± 1.5 vs 4.1 ± 1.8), pain interference (4.6 ± 1.8 vs 3.8 ± 1.7), and the overall health scale (60 ± 21 vs 71 ± 18). Well-being scores also significantly improved between baseline and 6 months F-UP (4.4 ± 2.1 vs 3.5 ± 2.8). Conclusions: Population-based data shows that cancer patients can benefit safely and effectively from MC as a complementary treatment, when prescribed and monitored under medical-nursing supervision.

Vigil, J. M., S. S. Stith, et al. (2017). "Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study." PLOS ONE **12**(11): e0187795.

Background Current levels and dangers of opioid use in the U.S. warrant the investigation of harm-reducing treatment alternatives. Purpose A preliminary, historical, cohort study was used to examine the association between enrollment in the New Mexico Medical Cannabis Program (MCP) and opioid prescription use. Methods Thirty-seven habitual opioid using, chronic pain patients (mean age = 54 years; 54% male; 86% chronic back pain) enrolled in the MCP between 4/1/2010 and 10/3/2015 were compared to 29 non-enrolled patients (mean age = 60 years; 69% male; 100% chronic back pain). We used Prescription Monitoring Program opioid records over a 21 month period (first three months prior to enrollment for the MCP patients) to measure cessation (defined as the absence of opioid prescriptions activity during the last three months of observation) and reduction (calculated in average daily intravenous [IV] morphine dosages). MCP patient-reported benefits and side effects of using cannabis one year after enrollment were also collected. Results By the end of the 21 month observation period, MCP enrollment was associated with 17.27 higher age- and gender-adjusted odds of ceasing opioid prescriptions (CI 1.89 to 157.36, p = 0.012), 5.12 higher odds of reducing daily prescription opioid dosages (CI 1.56 to 16.88, p = 0.007), and a 47 percentage point reduction in daily opioid dosages relative to a mean change of positive 10.4 percentage points in the comparison group (CI -90.68 to -3.59, p = 0.034). The monthly trend in opioid prescriptions over time was negative among MCP patients (-0.64mg IV morphine, CI -1.10 to -0.18, p = 0.008), but not statistically different from zero in the comparison group (0.18mg IV morphine, CI -0.02 to 0.39, p = 0.081). Survey responses indicated improvements in pain reduction, quality of life, social life, activity levels, and concentration, and few side effects from using cannabis one year after enrollment in the MCP (ps<0.001). Conclusions The clinically and statistically significant evidence of an association between MCP enrollment and opioid prescription cessation and reductions and improved quality of life warrants further investigations on cannabis as a potential alternative to prescription opioids for treating chronic pain.

Vilela, L. R., A. C. P. de Oliveira, et al. (2017). Chapter 63 - The Endocannabinoid System as a Target for New Antiseizure Drugs A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 606-615.

Abstract It has been suggested for centuries that Cannabis sativa may be effective in treating epilepsy. The scientific evidence, however, has remained surprisingly scant. Δ9-Tetrahydrocannabinol, the main active compound from this plant, and other phytocannabinoids (cannabidiol, Δ9-tetrahydrocannabivarin, and cannabidivarin), attenuates seizures in experimental animals, whereas synthetic cannabinoids induce inconsistent effects. The field has been advancing remarkably since the identification of the endocannabinoid system, comprising the CB1 (the main target of cannabinoids) and CB2 cannabinoid receptors, their endogenous ligands, anandamide and 2-arachidonoyl glycerol (endocannabinoids), and their metabolizing enzymes. The endocannabinoids act on-demand protecting the brain against excitotoxicity via CB1 receptor. Accordingly, inhibition of anandamide-hydrolysis attenuates neural activity and experimental seizures, representing an attractive pharmacological approach. Another potential strategy is blocking TRPV1 (vanilloid) channels, which are also activated by anandamide. The present text discusses critically the possible applications and limits of phytocannabinoids, synthetic cannabinoids, and endocannabinoid-hydrolysis inhibitors for the treatment of the epilepsies.

Vučković, S., D. Srebro, et al. (2018). "Cannabinoids and Pain: New Insights From Old Molecules." Frontiers in Pharmacology **9**: 1259.

Cannabis has been used for medicinal purposes for thousands of years. The prohibition of cannabis in the middle of the 20th century has arrested cannabis research. In recent years there is a growing debate about the use of cannabis for medical purposes. The term ‘medical cannabis’ refers to physician-recommended use of the cannabis herb and its components, called cannabinoids, to treat disease or improve symptoms. Chronic pain is the most commonly cited reason for using medical cannabis. Cannabinoids act via cannabinoid receptors, but they also affect the activities of many other receptors, ion channels and enzymes. Preclinical studies in animals using both pharmacological and genetic approaches have increased our understanding of the mechanisms of cannabinoid-induced analgesia and provided therapeutical strategies for treating pain in humans. The mechanisms of the analgesic effect of cannabinoids include inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve endings, modulation of postsynaptic neuron excitability, activation of descending inhibitory pain pathways, and reduction of neural inflammation. Recent meta-analyses of clinical trials that have examined the use of medical cannabis in chronic pain present a moderate amount of evidence that cannabis/cannabinoids exhibit analgesic activity, especially in neuropathic pain. The main limitations of these studies are short treatment duration, small numbers of patients, heterogeneous patient populations, examination of different cannabinoids, different doses, the use of different efficacy endpoints, as well as modest observable effects. Adverse effects in the short-term medical use of cannabis are generally mild to moderate, well tolerated and transient. Considering the serious health problems that arise in recreational use of cannabis, it is necessary to collect more information on the safety of long-term medical use of cannabis. Larger well-designed studies of longer duration are mandatory to determine the long-term efficacy and long-term safety of cannabis/cannabinoids and to provide definitive answers to physicians and patients regarding the risk and benefits of its use in the treatment of pain. Due to the limited efficacy and risk of serious adverse events, the use of cannabis/cannabinoids in the treatment of chronic pain should be reserved for refractory cases with mandatory monitoring of adverse effects.

Vulfsons, S., A. Minerbi, et al. (2020). "Cannabis and Pain Treatment-A Review of the Clinical Utility and a Practical Approach in Light of Uncertainty." Rambam Maimonides Med J **11**(1).

Over the past decade the phenomenon of cannabis as a legitimate form of treatment for pain has overwhelmed the medical community, especially in the field of pain. From a status of a schedule 1 substance having no currently accepted medical use and being considered to have high potential for abuse, its use has mushroomed to over 50,000 legal medical users per year in Israel alone. There appear to be many reasons behind this phenomenon-medical, sociological, and economical. Thus, what is cannabis? An abusive substance or a medication? Should it be incorporated into current biomedical practice, and how should it be administered? Finally, what is the evidence for the beneficial and detrimental effects of cannabis? This article reviews and discusses the current literature regarding the beneficial and the detrimental effects of medical cannabis in the treatment of pain. We further discuss the problems and challenges facing the medical community in this domain and offer a practical approach to deal with these challenges

Wadsworth, E., C. Leos-Toro, et al. (2020). "Mental Health and Medical Cannabis Use among Youth and Young Adults in Canada." Subst Use Misuse **55**(4): 582-589.

Background: In October 2018, Canada became the second country to legalize non-medical cannabis. However, medical cannabis has been legally available in Canada since 2001 and, in 2015, approximately 800,000 Canadians reported using cannabis for medical purposes. Mental health is a common reason reported for using medical cannabis. Objectives: The current study examined perceived mental health among four groups: (1) Non/ex-users; (2) Recent non-medical users; (3) Recent unauthorized medical users; and (4) Recent authorized medical users. Methods: A total of 867 Canadian cannabis users and nonusers aged 16 to 30 were recruited through an online consumer panel in 2017, one year before non-medical cannabis legalization. Logistic and multinomial regression models were fitted to examine differences among cannabis use status and mental health measures. All estimates represent weighted data. Results: Self-reported emotional and mental health problems were higher among unauthorized (83.9%) and authorized medical cannabis users (83.2%) compared to non-medical users and non/ex-users (44.5% and 39.5%, respectively). Medical users were more likely to report using cannabis to manage or improve mental health problems than non-medical users (p < .001). There were few differences between unauthorized and authorized medical users, and between non/ex-users and non-medical users. Conclusions: The findings highlight a discrepancy between the recommendation that individuals with some mental health problems should avoid cannabis and the widespread practice of using cannabis to manage mental health. Education and reduced stigma around using cannabis after legalization in Canada may help address users coming forwards regarding use of cannabis for mental health problems.

Wang, G. S., D. W. A. Bourne, et al. (2020). "Disposition of oral delta-9 tetrahydrocannabinol (THC) in children receiving cannabis extracts for epilepsy." Clin Toxicol (Phila) **58**(2): 124-128.

Introduction: Although over half of US states have legalized marijuana for medical indications, there is limited research in use in the pediatric population. The objective was to evaluate the disposition of oral tetrahydrocannabinol (THC) in children receiving cannabis extracts for pediatric epilepsy.Methods: Prospective, observational study, evaluating the disposition of oral THC in children receiving cannabis extracts. Subjects were less than 18 years of age, receiving oral cannabis for pediatric epilepsy. Subjects included in the study had at least 2 detectable THC and related metabolite plasma concentrations during serial blood draw over a 10-12 h study period.Results: Nine subjects with a median age of 11 years (IQR 4.75) were included in the study, with oral doses ranging from 0.02 mg/kg to 1.59 mg/kg. Peak plasma concentrations (0.8 to 3.6 ng/ml) in most patients were achieved within 2 hours, while acute phase elimination half-life ranged from 1 to 5 hours. THC-COOH and glucuronide remained elevated through the study period. There was significant variation between the dose ingested and peak concentrations (R(2) = 0.05).Conclusion: In pediatric patients receiving oral THC cannabis extracts, mean time to peak plasma concentrations was 2-7 hours, while mean acute phase elimination half-life was 4.0 hours. THC-COOH and THC-COOH glucuronide metabolites persisted throughout the 10-12 hour study period. Large variation and no correlation was noted between dose of THC by weight and peak concentrations, suggesting variation of bioavailability amongst pediatric population or inaccurate reporting of THC contents.

Warren, P. P., E. M. Bebin, et al. (2017). "The use of cannabidiol for seizure management in patients with brain tumor-related epilepsy." Neurocase **23**(5-6): 287-291.

ABSTRACTEpilepsy, commonly encountered by patients with brain tumors, is often refractory to standard therapies. Our aim was to examine the safety and efficacy of pharmaceutical grade cannabidiol (CBD; Epidiolex; Greenwich Biosciences) in those patients with epilepsy with concomitant tumors enrolled in The University of Alabama at Birmingham CBD Program (NCT02700412 and NCT02695537). Of the three patients with refractory seizures and a history of a primary brain tumor, two had improvement in seizure frequency and all three had improvement in seizure severity. These pilot results suggest that CBD should be further studied for the treatment of brain tumor-related epilepsy.

Weber, S. R. (2018). "Prescribing Substances of Abuse in Psychiatric Care." Psychiatric Times **35**(10): 25-26.

The article reviews the history of prescribing substances that can lead to addiction as treatment for mentally ill patients. Topics covered include the psychoanalyst Sigmund Freud's support of cocaine as a mental stimulant, opioids' use for depression treatment prior to antidepressant medications in the 1950s, and barbiturates' long-standing prescription as anxiolytics and hypnotics. Also noted are hallucinogens' use as an adjunctive treatment in psychotherapy.

Weiss, M., M. Buckley, et al. (2020). "A survey of cannabis use for symptom palliation in breast cancer patients by age and stage." Journal of Clinical Oncology **38**: 12108-12108.

12108 Background: Most US states have legalized medical cannabis for the treatment of serious conditions, including cancer. It is not well known which symptoms breast cancer patients seek to control with cannabis. Methods: Members of the Breastcancer.org and Healthline communities were invited to participate in this survey between 12/16/2019 and 1/19/2020. Eligibility criteria included age ≥18 years, resident of the US and a breast cancer diagnosis within the past 5 years. Eligible respondent data were analyzed for the symptomatic profile of cannabis users. Symptoms were compared between two groups using a Chi-square test of independence. The survey was led by Socanna, conducted by Outcomes Insights, and supported by a grant from Ananda Health/Ecofibre. Results: Among the 832 respondents who completed screening, 725 met the eligibility criteria, and 612 (84%) completed the survey. The median age of respondents was 57 years, and 85% had non-metastatic disease An estimated 42% of respondents have used medical cannabis to treat symptoms or side effects of breast cancer. Medical cannabis users reported using cannabis to treat insomnia (70%), joint and muscle aches, discomfort, stiffness, or pain (59%), anxiety (57%), and stress (51%). The medical cannabis users less than 50-year-old were more likely to use cannabis to treat these symptoms than their over 50-year-old counterparts, however, the differences were not statistically significant. Medical cannabis users under age 50 used cannabis significantly more than over 50 to treat nausea/vomiting (58% vs 40%; p = 0.010) and inflammation (34% vs 20%; p = 0.021). Medical cannabis users with metastatic disease were more likely to use medical cannabis to treat chronic pain 60% vs 41%; p = 0.017) than non-metastatic users. Post-surgery patients were most likely to use cannabis for nerve pain; and those who were beyond treatment, for stress. Patients suffered an average of 5 symptoms. Conclusions: A significant proportion of breast cancer patients reported using cannabis to treat a combination of symptoms from their cancer and its treatment. Although younger patients are somewhat more likely to use this form of palliative management, older patients are suffering from the same symptoms and their use is nearly as high. More research is needed on the personalization of safe and effective symptomatic management with medical cannabis, for people of all ages, stages, and forms of treatment.

Weiss, M., J. Hibbs, et al. (2020). "A survey of breast cancer patients’ use of cannabis before, during, and after treatment." Journal of Clinical Oncology **38**: e19210-e19210.

e19210 Background: The availability of cannabis is rapidly expanding and cancer is a qualifying condition in all states allowing medical cannabis. However, there are many unknowns with respect to patterns of cannabis use among breast cancer patients. The goal of this study was to better understand how and when cannabis is used among breast cancer patients. Methods: Between 12/16/2019 and 1/19/2020, U.S.-based members of Breastcancer.org and the Healthline communities were invited to participate in a cannabis survey. Subjects confirmed they were age ≥18 and diagnosed with breast cancer within 5 years. After informed consent, data were collected, de-identified and analyzed in aggregate. The study was led by Socanna, conducted by Outcomes Insights, and supported by a grant from Ananda Health/Ecofibre. Results: A total of 3522 persons initiated screening, 832 completed screening, and 725 met eligibility criteria, of whom 612 completed the survey (84%). The results showed that 42% of participants had used medical cannabis products to relieve symptoms, including insomnia (70%), pain (59%), anxiety (57%), stress (51%), and nausea/vomiting (46%). Additionally, cannabis was used prior to treatment in 24%, during treatment in 79%, and after treatment in 54%. Of subjects reporting cannabis use during treatment: 86% used it during chemotherapy, 71% during HER2 therapy, 65% during hormonal therapy, 49% during breast radiation, and 47% during radiation for metastatic sites. Post-surgical use was reported in 51% after mastectomy alone, 40% after lumpectomy, and 38% after mastectomy/reconstruction. An average of 3-4 cannabis products were utilized. Products were sourced from medical dispensaries (54%), family/friends (33%), and recreational sources (27%). Although cannabis using subjects strongly preferred medical sources, 77% had also utilized recreational sources. Conclusions: This survey shows that almost half of breast cancer patients reported using cannabis to help relieve common symptoms from breast cancer or its treatments. Of those, 79% used cannabis during active treatment, which can impact efficacy and safety. To date, studies have not investigated drug interactions between cannabis and these therapeutic agents. Furthermore, there is a concern regarding contaminants. Although most medical cannabis is tested for pathogens and contaminants, this is not the case for cannabis obtained from other sources. The results of this study highlight the need for research regarding cannabis for medical purposes, including safety and interaction studies.

Wendelboe, A., R. Mathew, et al. (2019). "Is There Less Opioid Abuse in States Where Marijuana Has Been Decriminalized, Either for Medicinal or Recreational Use? A Clin-IQ." Journal of Patient-Centered Research and Reviews 6: 267-273.

Opioid use, abuse, and associated mortality have reached an epidemic level. In some states, cannabis is being used to treat chronic pain. To examine the hypothesis that medical marijuana legislation may reduce adverse opioid-related outcomes if patients substitute cannabis for opioids for pain management, we conducted a clinical inquiry (Clin-IQ). We searched Ovid MEDLINE, Ovid MEDLINE In-Process, and Embase for studies using the search terms marijuana, cannabis, legal, marijuana smoking, medical marijuana, opioid-related disorders, cannabis use, medical cannabis, legal aspect, and opiate addiction. We included population-based articles published from January 1, 2012, through December 5, 2018, that assessed the relationship between marijuana use and decriminalization and the aforementioned opioid-related outcomes. Ten peer-reviewed studies met the inclusion criteria; 3 cross-sectional studies, 6 ecologic studies (ie, using aggregate data), and 1 retrospective cohort study. Eight studies reported associations between policies decriminalizing marijuana and reduced prescription opioid use, 1 study was inconclusive, and the retrospective cohort study reported an increase in adverse opioid-related outcomes. These results should be interpreted with caution given limitations associated with the studies’ design. Results demonstrating association between marijuana decriminalization and opioid-related outcomes are mixed. Longitudinal studies are needed, and further analysis of this policy should continue to be tracked.

Wheless, J. W., D. Dlugos, et al. (2019). "Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy." CNS Drugs 33(6): 593-604.

BACKGROUND: Prior studies have evaluated the use of various constituents of cannabis for their anti-seizure effects. Specifically, cannabidiol, a non-psychoactive component of cannabis, has been investigated for treatment-resistant epilepsy, but more information is needed particularly on its use in a pediatric population. OBJECTIVE: The objective of this study was to evaluate the pharmacokinetics and safety of a synthetic pharmaceutical-grade cannabidiol oral solution in pediatric patients with treatment-resistant epilepsy. METHODS: In this open-label study, pediatric patients (aged 1 to </= 17 years) with treatment-resistant epilepsy received cannabidiol oral solution administered as add-on to their current antiepileptic drug regimen. Patients received a single dose (5, 10, or 20 mg/kg) on day 1 and twice-daily dosing on days 4 through 10 (10-mg/kg [cohort 1], 20-mg/kg [cohort 2], or 40-mg/kg [cohort 3] total daily dose). Serial blood samples were collected on day 1 before dosing and up to 72 h post-dose, and on day 10 before dosing and up to 24 h post-dose. Blood samples to assess trough concentrations of cannabidiol were collected on day 6 (for patients aged 12 to </= 17 years), day 8 (for patients aged 2 to </= 17 years), and day 9 (for patients aged 6 to </= 17 years). RESULTS: Overall, 61 patients across three cohorts received one of three doses of cannabidiol oral solution (mean age, 7.6 years). The age composition was similar in the three cohorts. There was a trend for increased cannabidiol exposure with increased cannabidiol oral solution dosing, but overall exposure varied. Approximately 2-6 days of twice-daily dosing provided steady-state concentrations of cannabidiol. A bi-directional drug interaction occurred with cannabidiol and clobazam. Concomitant administration of clobazam with 40 mg/kg/day of cannabidiol oral solution resulted in a 2.5-fold increase in mean cannabidiol exposure. Mean plasma clobazam concentrations were 1.7- and 2.2-fold greater in patients receiving clobazam concomitantly with 40 mg/kg/day of cannabidiol oral solution compared with 10 mg/kg/day and 20 mg/kg/day. Mean plasma norclobazam values were 1.3- and 1.9-fold higher for patients taking clobazam plus 40 mg/kg/day of cannabidiol oral solution compared with the 10-mg/kg/day and 20-mg/kg/day groups. All doses were generally well tolerated, and common adverse events that occurred at > 10% were somnolence (21.3%), anemia (18.0%), and diarrhea (16.4%). CONCLUSIONS: Inter-individual variability in systemic cannabidiol exposure after pediatric patient treatment with cannabidiol oral solution was observed but decreased with multiple doses. Short-term administration was generally safe and well tolerated. TRIAL REGISTRATION: ClinicalTrials.gov (NCT02324673).

Wolfe, D., K. Corace, et al. (2020). "Effects of medical and non-medical cannabis use in older adults: protocol for a scoping review." BMJ Open **10**(2): e034301.

Introduction With its legalisation and regulation in Canada in 2018, the proportion of Canadians reporting cannabis use in 2019 increased substantially over the previous year, with half of new users being aged 45+ years. While use in older adults has been low historically, as those born in the 1950s and 1960s continue to age, this demographic will progressively have more liberal attitudes, prior cannabis exposure and higher use rates. However, older adults experience slower metabolism, increased likelihood of polypharmacy, cognitive decline and chronic physical/mental health problems. There is a need to enhance knowledge of the effects of cannabis use in older adults. The following question will be addressed using a scoping review approach: what evidence exists regarding beneficial and harmful effects of medical and non-medical cannabis use in adults >50 years of age? Given that beneficial and harmful effects of cannabis may be mediated by patient-level (eg, age, sex and race) and cannabis-related factors (eg, natural vs synthetic, consumption method), subgroup effects related to these and additional factors will be explored.Methods and analysis Methods for scoping reviews outlined by Arksey &amp; O’Malley and the Joanna Briggs Institute will be used. A librarian designed a systematic search of the literature from database inception to June 2019. Using the OVID platform, Ovid MEDLINE will be searched, including Epub Ahead of Print and In-Process and Other Non-Indexed Citations, Embase Classic+Embase, and PsycINFO for reviews, randomised trials, non-randomised trials and observational studies of cannabis use. The Cochrane Library on Wiley will also be searched. Eligibility criteria will be older adult participants, currently using cannabis (medical or non-medical), with studies required to report a cannabis-related health outcome to be eligible. Two reviewers will screen citations and full texts, with support from artificial intelligence. Two reviewers will chart data. Tables/graphics will be used to map evidence and identify evidence gaps.Ethics and dissemination This research will enhance awareness of existing evidence addressing the health effects of medical and non-medical cannabis use in older adults. Findings will be disseminated through a peer-reviewed publication, conference presentations and a stakeholder meeting.Trial registration number DOI 10.17605/OSF.IO/5JTAQ.

Wong, E. and S. I. Ranapurwala (2019). "Cardiovascular Risk Associated with Medical Use of Opioids and Cannabinoids: A Systematic Review." Current Cardiovascular Risk Reports 13(10): 30.

The long-term use of opioid and cannabinoid medications to control chronic pain and treat opioid use disorders now involves a large proportion of the population in the United States. Yet, the cardiovascular risks of opioids are not well understood. This systematic review summarizes the current literature to assess the potential cardiovascular disease risks associated with opioid and cannabinoid medications.

Wong, S. S. and T. E. Wilens (2017). Medical Cannabinoids in Children and Adolescents: A Systematic Review.

Context: Legalization of medical marijuana in many states has led to a widening gap between the accessibility and the evidence for cannabinoids as a medical treatment. Objective: To systematically review published reports to identify the evidence base of cannabinoids as a medical treatment in children and adolescents. Data sources: Based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a search of PubMed, Medline, and the Cumulative Index to Nursing and Allied Health Literature databases was conducted in May 2017. Study selection: Searching identified 2743 citations, and 103 full texts were reviewed. Data extraction: Searching identified 21 articles that met inclusion criteria, including 22 studies with a total sample of 795 participants. Five randomized controlled trials, 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series were identified. Results: Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for epilepsy. At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, and Tourette syndrome. Limitations: The methodological quality of studies varied, with the majority of studies lacking control groups, limited by small sample size, and not designed to test for the statistical significance of outcome measures. Studies were heterogeneous in the cannabinoid composition and dosage and lacked long-term follow-up to identify potential adverse effects. Conclusions: Additional research is needed to evaluate the potential role of medical cannabinoids in children and adolescents, especially given increasing accessibility from state legalization and potential psychiatric and neurocognitive adverse effects identified from studies of recreational cannabis use.

Workman, C. D., J. H. Kindred, et al. (2019). "The Effects of Chronic Δ-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) use on Cerebral Glucose Metabolism in Multiple Sclerosis: A Pilot Study." Applied Physiology, Nutrition, and Metabolism.

ABSTRACT

This exploratory pilot study investigated the effects of chronic Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on cerebral glucose metabolism in people with multiple sclerosis (PwMS). Compared to non-users, THC-users had hypermetabolism of three regions (p < 0.039, d >1.17) in left temporal areas, while CBD-users had hypometabolism of five regions (p < 0.032, d > 1.31) in left temporal areas. This study highlights the need to discriminate between THC and CBD in future cannabis studies. Novelty: • Chronic THC and CBD use had disparate effects on cerebral glucose metabolism in PwMS.

Wright, N. E., K. E. Maple, et al. (2017). Chapter 16 - Effects of Cannabis Use on Neurocognition in Adolescents and Emerging Adults A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 151-159.

Abstract Adolescent cannabis use has substantially increased over the past two decades. Teens and young adults are undergoing considerable neurodevelopment, and thus may be particularly susceptible to the negative effects of cannabis. This chapter will cover the potential consequences of cannabis use on the developing brain, including neurocognition, brain structure, and brain function. We will also address how additional factors, including gender, age of use onset, and other substance use, may moderate the effects of cannabis on individuals. We will highlight that more research is needed to disentangle preexisting differences from the effects of cannabis use, as well as how cannabis use may affect special populations, such as, those with psychiatric comorbidities. Given the high rates of use, and research suggesting negative outcomes, policy makers should target efforts toward teen cannabis use prevention.

Wright, P., Z. Walsh, et al. (2020). "Canadian clinical practice guidelines for the use of plant-based cannabis and cannabinoid-based products in the management of chronic non-cancer pain and co-occurring conditions: protocol for a systematic literature review." BMJ Open **10**(5): e036114.

Introduction Chronic pain and co-occurring disorders, such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders, are among the most common conditions for which cannabis and cannabinoid-based products derived from the cannabis plant (CBP) are used for therapeutic purposes. However, healthcare providers report that they lack sufficient information on the risks, benefits and appropriate use of cannabis and CBP derived from the cannabis plant for therapeutic purposes.Methods and analysis We will conduct a systematic review of studies investigating the use of cannabis and CBP derived from the cannabis plant for the treatment of chronic pain and co-occurring conditions. Randomised controlled trials, meta-analyses and observational studies will be prioritised. We will exclude reviews of cannabinoid mechanisms of actions, commentary articles and narrative reviews. The primary outcome of interest will be efficacy in relieving chronic pain. Secondary outcomes will be efficacy in ameliorating conditions such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders. We will search electronic bibliographic databases including Academic Search Complete, Cochrane Database of Systematic Reviews, Evidence based Medicine Reviewes, OVID Medline, PsychINFO, PubMed, CINAHL and Web of Science. Two reviewers will conduct screening and data collection independently. Study level of bias will be assessed using the Cochrane Risk of Bias Assessment Tool for randomised controlled trials and non-randomised studies. Narrative analysis will be utilised to interpret the data.Ethics and dissemination The results of this systematic review will inform guideline development for the use of cannabis and CBP derived from the cannabis plant in the management of chronic pain and co-occurring conditions. Areas requiring further study will also be highlighted.PROSPERO registration number CRD42020135886.

Young, D. C., J. Jae-Woo, et al. (2019). "Edmonton Symptom Assessment Scale and Clinical Characteristics Associated With Cannabinoid Use in Oncology Supportive Care Outpatients." Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw 17(9): 1059-1064.

Background: Information about the frequency of cannabinoid use and the clinical characteristics of its users in oncology supportive care is limited. This study explored associations between cannabinoid use and cancer-related clinical characteristics in a cancer population. Patients and Methods: This retrospective review included 332 patients who had a urine drug test (UDT) for tetrahydrocannabinol (THC) together with completion of an Edmonton Symptom Assessment Scale (ESAS) and cannabinoid history questionnaire on the same day that urine was obtained during 1 year in the supportive care clinic. Results: The frequency of positive results for THC in a UDT was 22.9% (n=76). Significant statistical differences were seen between THC-positive and THC-negative patients for age (median of 52 [lower quartile, 44; upper quartile, 56] vs 58 [48; 67] years; P<.001), male sex (53.9% vs 39.5%; P=.034), and past or current cannabinoid use (65.8% vs 26.2%; P<.001). Statistical significance was observed in ESAS items between the THC-positive and THC-negative groups for pain (7 [lower quartile, 5; upper quartile; 8] vs 5 [3; 7]; P=.001), nausea (1 [0; 3] vs 0 [0; 3]; P=.049), appetite (4 [2; 7] vs 3 [0; 5.75]; P=.015), overall well-being (5.5 [4; 7] vs 5 [3; 6]; P=.002), spiritual well-being (5 [2; 6] vs 3 [1; 3]; P=.015), insomnia (7 [5; 9] vs 4 [2; 7]; P<.001), and total ESAS (52 [34; 66] vs 44 [29; 54]; P=.001). Among patients who reported current or past cannabinoid use, THC-positive patients had higher total scores and scores for pain, appetite, overall well-being, spiritual well-being, and insomnia than THC-negative patients. Conclusions: Patients with cancer receiving outpatient supportive care who had positive UDT results for THC had higher symptom severity scores for pain, nausea, appetite, overall and spiritual well-being, and insomnia compared with their THC-negative counterparts. These results highlight potential opportunities to improve palliative care

Zalman, D. and G. Bar-Sela (2017). Chapter 89 - Cannabis and Synthetic Cannabinoids for Cancer Patients: Multiple Palliative Indications Together With Promising Laboratory Antineoplastic Effects A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** 859-868.

Abstract The medical and social applications of cannabis and its derivatives are well known in history, but only recently has a renascence of its medical use arrived. In parallel with the rediscovery of the pathophysiology and possible uses of the cannabis plant, the palliative approach was assimilated, and cannabis was caught in the spotlight. Nevertheless, we still lack sufficient medical data to support its extensive use for symptom relief, or to confirm its perceived safety. Controlled trials are needed to confirm or deny what is now comprehensible only to the public and medical community. In this chapter, we shall review the available clinical information regarding the clinical implications for cannabinoids use in palliative cancer medicine, according to avid literature. We also summarize some of the laboratory data regarding the plant’s antineoplastic efficacy.

Zarhin, D., M. Negev, et al. (2019). "“Medical Cannabis” as a Contested Medicine: Fighting Over Epistemology and Morality." Science, Technology, & Human Values **45**(3): 488-514.

Few empirical studies have explored how different types of knowledge are associated with diverse objectivities and moral economies. Here, we examine these associations through an empirical investigation of the public policy debate in Israel around medical cannabis (MC), which may be termed a contested medicine because its therapeutic effects, while subjectively felt by users, are not generally recognized by the medical profession. Our findings indicate that beneath the MC debate lie deep-seated issues of epistemology, which are entwined with questions of ethics and morality. Whereas some stakeholder groups viewed evidence-based medicine and mechanical objectivity as the only valid knowledge base, others called for recognition of a particular experience-based knowledge, championing regulatory, administrative, or strong objectivity. Stakeholders? interpretations of what should be considered as ethical courses of (in)action corresponded to their epistemological views, with most criticizing the regulators for relying on regulatory subjectivity instead of objectivity. Our in-depth mapping of this arena allowed us not only to shed light on the emergence of the new entity called ?medical cannabis? but also to reexamine the link between epistemology, ethics, and action and to elucidate how heterogeneous groups view the validity and objectivity of knowledge and the interface between medicine, science, and policy.

Zarrabi, A. J., J. W. Welsh, et al. (2020). "Perception of Benefits and Harms of Medical Cannabis among Seriously Ill Patients in an Outpatient Palliative Care Practice." J Palliat Med **23**(4): 558-562.

Introduction: Patients with serious illness often have pain, uncontrolled symptoms, and poor quality of life. Evidence continues to evolve regarding the role of cannabis to treat chronic pain, nausea, and anorexia. Little is known about how patients with serious illness perceive its benefits and harms. Given that an increasing number of clinicians across the United States are treating patients with medical cannabis, it is important for providers to understand patient beliefs about this modality. We assessed patient perceptions of benefits and harms of cannabis who obtained a medical cannabis card within an ambulatory palliative care (APC) practice. Methods: We recruited patients with a medical cannabis card, allowing for legal possession of cannabis oil, from an APC practice in Georgia. All participants reported using cannabis products. Patients completed an online survey that included questions about their cannabis use, concurrent opiate or controlled medication use, and perceptions of benefits and harms of cannabis. Results: All 101 patients invited to participate completed the survey. A majority had cancer (76%) and were married (61%), disabled or retired (75%), older than 50 years of age (64%), and men (56%). Most patients ingested (61%) or vaporized (49%) cannabis products. A majority of respondents perceived cannabis to be important for their pain (96%) management. They reported that side effects were minimally bothersome, and drowsiness was the most commonly reported bothersome harm (28%). A minority of patients reported cannabis withdrawal symptoms (19%) and concerns for dependency (14%). The majority of patients were using concurrent prescription opioids (65%). Furthermore, a majority of cancer patients reported cannabis as being important for cancer cure (59%). Conclusion: Patients living with serious illnesses who use cannabis in the context of a multidisciplinary APC practice use cannabis for curative intent and for pain and symptom control. Patients reported improved pain, other symptoms, and a sense of well-being with few reported harms.

Zeyl, V., K. Sawyer, et al. (2020). "What Do You Know About Maryjane? A Systematic Review of the Current Data on the THC:CBD Ratio." Subst Use Misuse **55**(8): 1223-1227.

Background: Ratios of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) impact metabolism and therapeutic effects of cannabis. Currently, no states with legalized medical or recreational cannabis consider ratios THC:CBD in regulations. Objective: Determine what THC:CBD ratios are selected for use in clinical cannabis trials and what is the rationale. Methods: This is a systematic literature review of Central, CINAHL, Embase, PsycInfo, and PubMed of the last 10 years of English language medical cannabis publications highlighting THC:CBD ratios. Included were clinical studies of products containing and listing both THC and CBD ratios, percentages, or weighted amounts. Case reports and series, abstracts, reviews, and meta-analysis were excluded. Non-human, non-therapeutic, or studies examining approved cannabis pharmaceuticals were excluded. Results: Four hundred and seventy-nine (479) unique references were found, of which 11 met inclusion criteria. THC:CBD ratios listed and/or calculated: 1:0, 22:1, 2:1, 1:1, 1:2, 1:6, 1:9, 1:20, 1:33, 1:50, and 0:1. Rationale for ratios selected was often not listed, or simply trivialized as the ratios available to patients in the area, or ratios that were pharmaceutically available throughout the study country. One study compared ratios of high and low THC:CBD, but did not specify the ratios. Conclusion: The medical and scientific communities have not drawn substantive conclusions nor thoroughly explored THC:CBD ratios for "best practice" treatment of different disease processes and their sequelae. While there is evidence that cannabis provides medical benefits, research is lacking on standardization of medical cannabis use in modern medical practices.

Zgair, A., J. B. Lee, et al. (2017). "Oral administration of cannabis with lipids leads to high levels of cannabinoids in the intestinal lymphatic system and prominent immunomodulation." Scientific Reports **7**(1): 14542.

Cannabidiol (CBD) and ∆9-tetrahydrocannabinol (THC) have well documented immunomodulatory effects in vitro, but not following oral administration in humans. Here we show that oral co-administration of cannabinoids with lipids can substantially increase their intestinal lymphatic transport in rats. CBD concentrations in the lymph were 250-fold higher than in plasma, while THC concentrations in the lymph were 100-fold higher than in plasma. Since cannabinoids are currently in clinical use for the treatment of spasticity in multiple sclerosis (MS) patients and to alleviate nausea and vomiting associated with chemotherapy in cancer patients, lymphocytes from those patients were used to assess the immunomodulatory effects of cannabinoids. The levels of cannabinoids recovered in the intestinal lymphatic system, but not in plasma, were substantially above the immunomodulatory threshold in murine and human lymphocytes. CBD showed higher immunosuppressive effects than THC. Moreover, immune cells from MS patients were more susceptible to the immunosuppressive effects of cannabinoids than those from healthy volunteers or cancer patients. Therefore, administering cannabinoids with a high-fat meal or in lipid-based formulations has the potential to be a therapeutic approach to improve the treatment of MS, or indeed other autoimmune disorders. However, intestinal lymphatic transport of cannabinoids in immunocompromised patients requires caution.

Zolotov, Y., S. Vulfsons, et al. (2018). "Medical cannabis: An oxymoron? Physicians perceptions of medical cannabis." International Journal of Drug Policy **57**: 4-10.

Background: Medical cannabis policies are changing in many places around the world, and physicians play a major role in the implementation of these policies. The aim of this study was to gain a deeper understanding of physicians? views on medical cannabis and its possible integration into their clinic, as well as to identify potential underlying factors that influence these perceptions.

Zuardi, A. W., J. A. de Souza Crippa, et al. (2017). Chapter e13 - The Anxiolytic Effects of Cannabidiol (CBD) A2 - Preedy, V.R. Handbook of Cannabis and Related Pathologies. San Diego, Academic Press**:** e131-e139.

Abstract The objectives of the present chapter are to review and describe the studies made on cannabidiol (CBD), a nonpsychotomimetic constituent of the Cannabis sativa plant, as an anxiolytic compound, and to discuss its possible mechanisms of action. The papers selected for the chapter were identified through systematic searches in the main electronic databases, and the reference lists of the included articles, review publications, and book chapters were hand-searched for additional references. We included both experimental laboratory animal and human studies. Taken together, the studies assessed in the present chapter clearly suggest an anxiolytic-like effect of CBD, both in animal models and in healthy volunteers. In addition, this cannabinoid was shown to decrease anxiety in patients with social phobia. Novel clinical trials involving patients with other anxiety disorders, such as panic, obsessive-compulsive, social anxiety, and posttraumatic stress disorders are now necessary and opportune. However, the optimal therapeutic window of CBD and the mechanisms involved in its anxiolytic action remain to be determined.

Zylla, D. M., J. Eklund, et al. (2019). "A randomized trial of medical cannabis (MC) in patients with advanced cancer (AC) to assess impact on opioid use and cancer-related symptoms." Journal of Clinical Oncology 37(31\_suppl): 109-109.

109Background: Higher pain and greater long-term opioid requirements have been associated with shorter survival and decreased quality of life (QOL) in patients with AC. Routine use of MC is limited by a lack of rigorous scientific data and concerns about side effects, legal ramifications, and cost. Methods: 30 patients with stage IV cancer requiring opioids were randomized 1:1 to early cannabis (EC, n=15) vs. delayed cannabis (DC, n=15). The EC group was provided with 3 months (3M) of MC at no charge, while the DC group received standard oncology care without MC for the first 3M. Patients met with licensed pharmacists at one of two MC manufacturers to determine optimal MC dosing, formulation, and route. Patients completed monthly pain logs, opioid/MC logs, and validated Patient-Reported Symptom Monitoring surveys. Results: A higher proportion of EC patients achieved a reduction in opioid use and improved pain control. On average over a 3M window, EC patients did not require opioid dose escalation, had lower mean pain, and had similar QOL compared to DC patients. Estimated mean daily THC and CBD dose at 3M was 76 mg (range 5-186 mg) and 36 mg (range <1-516 mg), respectively. Mean perceived benefit of MC was 5.1 and mean perceived negative impact was 2.7 (1 = no benefit/negative effects, 7 = a great deal of benefit/negative effects). 33% of patients died during the anticipated 6-month study period and patient compliance with study logs limited analysis. Conclusions: Randomized studies of MC in the oncology setting are feasible, but rigorous data collection is challenging. The addition of MC to standard oncology care in patients with AC was well-tolerated and may lead to improved pain control and lower opioid requirements. Main Results.EC (n = 12)aDC (n = 8)aMedian age (range)58 (38-76)53 (47-77)% female5850Median days since stage IV diagnosis (range)136 (12-3755)334 (43-1533)Mean pain, 0-10 b5.3 | 4.76.1 | 6.0Mean personalized pain level goal (PPG) b3.4 | 3.04.1 | 3.8% meeting PPG b25 | 4438 | 13Mean daily oral morphine equivalents (MDOME) b55 | 5435 | 67% with ≥20% reduction in MDOME at 3M440a Patient totals per group vary for certain measures, based on available datab Formatted as Baseline | 3M

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