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PAIN MANAGEMENT (S MACE, SECTION EDITOR)

Cannabinoids and Pain Management: an Insight into Recent Advancements

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Abstract

Purpose of Review 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.

Recent Findings Current research suggests that a potential role exists for medical cannabis in pain management, although research shows varied effectiveness by the type of pain. Moreover, its coadministration with opioids may result in reduced opioid requirements.

Summary Patients with neuropathic pain, cancer pain, and migraine headache may benefit from the analgesic effects of a cannabis-based medicine (CBM), but not necessarily patients with chronic abdominal pain. Equivocal results were shown in fibromyalgia and postoperative orthopedic pain. Interestingly, the opioid-sparing properties of CBM make it an attractive option for pain management. However, the scale and quality of studies conducted are limited. Further research is necessary to establish recommendation guidelines for medical cannabis in pain management.

Keywords Cannabinoids and pain · THC and pain · Tetrahydrocannabinol and pain · Cannabis and pain · Marijuana and pain

Introduction

Cannabis sativa, one of the world's oldest cultivated plants, has been used over centuries for medicinal purposes [1]. It is indigenous to Central Asia but cultivated worldwide. The dried flowers (marijuana), fiber (hemp), resin (hashish), and oil have all been used in the treatment of pain. Historians have provided promising clues to potential treatment with cannabis for a wide array of medical syndromes including chronic pain, spasticity, cancer, seizure disorders, nausea, anorexia, and infectious disease, but the scientific basis for its medicinal effectiveness remains unclear [1, 2••].

In the USA, currently, 34 states, the District of Columbia, and the US territories of Guam, Puerto Rico, and the US Virgin Islands have approved medical marijuana/cannabis programs [3]. The majority of these programs include chronic pain as one of the approved conditions for which cannabis may be used. Indeed, pain relief is the most frequently cited reason for the medical use of cannabis [4–6], and medicinal cannabis registries typically report pain as the most common reason for its use [7].

Although the therapeutic potential of cannabinoids in current pain management remains uncertain, many patients report that cannabis has helped to alleviate their pain [8]. Individuals suffering from chronic pain and a variety of chronic illnesses (e.g., seizure disorders, cancer, glaucoma, multiple sclerosis, AIDS wasting syndrome) have reported that smoking marijuana improved their conditions when standard treatments did not [4]. The National Academies Committee on the Health Effects of Marijuana recently reported that there is "conclusive or substantial evidence" that cannabis is effective for the treatment of chronic pain in adults [9].

Although over 80 cannabinoids have been isolated from *Cannabis sativa*, cannabidiol (CBD), which has a lower psychoactive profile, and Delta-9-tetrahydrocannabinol (THC),

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which has a higher psychoactive profile, are the most abundant. Plants have been cultivated to contain different amounts of CBD and THC in order to attempt to modulate its psychoactive effects, with higher THC content favored in the black market to produce a greater "high." Inhalation (drawing into the lungs) or vaping (holding the smoke in one's mouth without necessarily inhaling) produces the fastest effect, with absorption taking place within a few minutes. These compounds both bind to endogenous receptors in the body, the most common of which are CB1 and CB2, both g-protein-coupled receptors [10–12]. CB1 receptors are most densely present in the central nervous system, and THC has a higher affinity for these receptors [13–15]. CB2 receptors are expressed in high quantities in human immune tissues and cells, e.g., in the spleen, tonsils, and leukocytes. Aside from potential direct analgesic effects, cannabis is also postulated to modulate serotonin and opioid receptors to treat pain through possible synergistic interactions with opioid analgesics, or by improving the efficacy of pain treatment in patients with tolerance to opioids, although this mechanism is less clear [16].

As medicinal cannabis laws change in the USA, an increasing number of patients may have questions regarding its use. Healthcare professionals should be educated on the most recent data and be prepared to answer questions regarding cannabis use appropriateness for use in treatment [17]. This review focuses on the recent advancements in research on cannabinoids and pain.

Methods

We performed a PubMed database search on June 6, 2019, using the keywords "Cannabis + pain," "Cannabis or tetrahydrocannabinol+ cancer pain," "Cannabis or tetrahydrocannabinol or THC + neuropathic pain," "Cannabis or tetrahydrocannabinol or THC + migraine or headache," "Cannabis or tetrahydrocannabinol or THC + fibromyalgia," "Cannabis or tetrahydrocannabinol or THC + abdominal pain," and "Cannabis or tetrahydrocannabinol or THC + postoperative or surgery + pain." The search was mainly limited to clinical studies and comparative studies published in the last 5 years (2015–2019) with an exception for cancer pain studies for which the search was extended to 7 years because of limited recent data availability. The search included only manuscripts published in English.

Results

Of the 19 studies that met the criteria, we reviewed these based on the role of cannabis in relation to cancer pain, neuropathic pain, fibromyalgia, headache, visceral pain, orthopedic surgery postoperative pain management, failed back syndrome pain management, and coadministration with opioids.

Role in Cancer Pain

Pain is common in cancer patients, particularly in the advanced stage of disease when the prevalence is estimated to be more than 70% [18]. Chronic and unrelieved cancer-related pain can cause significant distress and disability. Patients with cancer may experience pain due to the cancer itself, as a side effect of cancer treatment, or as a result of other comorbid diseases. In patients with cancer-related pain, compounds derived from the plant species *Cannabis sativa* L., such as those with psychoactive THC and non-psychoactive cannabidiol (CBD), may demonstrate the potential to alleviate pain; however, its role is unclear.

Cannabis has been studied in the management of advanced cancer-related pain. In two-phase 3, double-blind, randomized, placebo-controlled trials, Fallon et al. assessed the analgesic efficacy of adjunctive nabiximols (tradename Sativex, an oral mucosal spray containing THC, 27 mg/mL and CBD, 25 mg/mL) in advanced cancer patients with cancer-related pain not alleviated by optimized opioid therapy. Neither of these studies found a decrease in pain as measured by the numeric rating scale (NRS) with nabiximols, although there was an improvement noted in some quality of life measures [18].

Huser et al. performed a systematic review and meta-analysis of randomized controlled trials to evaluate the use of oromucosal nabiximols and THC for patients with cancer pain, and found no conclusive evidence that cannabinoids alleviate pain better than placebo. They also concluded that the evidence available is of low quality [19].

Others have found different results. Aviram et al. [20] performed a systematic review and meta-analysis to assess the efficacy of cannabis-based medicines (CBMs) in pain management. To examine the effects of CBMs on cancer pain, they conducted a separate meta-analysis of three RCTs that examined cancer pain directly, finding moderate effect sizes for cancer pain relief showing more benefit for CBM over placebo [20]. Similarly, Bar-Sela et al. [21] found not only a reduction in pain but also a decreased use of pain medications and anxiolytics in a significant portion of patients. Although limited by the observational design and self-reporting outcomes, the study's findings of improvement in symptoms are noteworthy to support the consideration of cannabis in the practice of oncology palliative treatment [21].

Another study with promising results in favor of cannabis-based medicines for pain management was by Portenoy et al. [22]. This randomized, double-blind, placebo-controlled, graded-dose study in patients with advanced cancer and opioid-refractory pain examined nabiximols versus placebo. The study found improvement in pain with low and medium dose cannabinoids, while intolerable side effects were noted in the highest dose group [22]. Similarly, Johnson et al. [23] performed an open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal

spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. The study showed that the long-term use of THC/CBD spray was well tolerated, with no evidence of tolerance over time, as can be seen in long-term opioid use. Furthermore, patients who kept using the study medication did not seek to increase their pain medication doses over time, suggesting that the adjuvant use of cannabinoids in cancer-related pain could provide useful benefit [23].

Role in Neuropathic Pain

Neuropathic pain, generally considered a difficult condition to treat, arises from nerve damage to sensory or spinal nerves, which send inaccurate pain messages to higher centers [24]. Whiting et al. performed a systematic review and meta-analysis of cannabinoids for medical use which examined 28 randomized trials among 2454 patients with chronic pain. The research indicated that, compared with placebo, cannabinoids were associated with a greater reduction in pain and a greater average reduction in numerical pain. The investigators concluded that there was moderate evidence to support the use of cannabinoids for the treatment of chronic pain, with neuropathy as the most commonly cited source of chronic pain [25].

Favorable findings were also reported by Wallace et al. [26] who performed a small, short-term, placebo-controlled trial on 16 patients of inhaled aerosolized cannabis with four different strengths of THC. The study demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain among patients with treatment-refractory pain [26].

Wilsey et al. [27] conducted a randomized, placebo-controlled crossover trial utilizing vaporized cannabis containing placebo and 6.7% and 2.9% THC among 42 participants with central neuropathic pain related to spinal cord injury and disease. Results indicated that vaporized cannabis reduced neuropathic pain scale ratings, but after false-discovery-rate-adjusted (FDR) *P*-values, there was no evidence of a dose-dependent effect [27].

Role in Fibromyalgia

Fibromyalgia is characterized by chronic widespread pain, often accompanied by secondary symptoms including sleep disturbance, tiredness, and cognitive symptoms such as memory deficits, known as "fibro-fog" [28]. Fibromyalgia pain is generally considered difficult to treat medically, with conventional pharmacologic treatment only mildly effective [29].

van de Donk et al. performed an experimental, randomized, placebo-controlled, 4-way crossover trial to assess the analgesic effects of inhaled pharmaceutical-grade cannabis in 20 patients with fibromyalgia-related chronic pain. The study looked at 4 different medications with known THC/CBD ratios. Subjects receiving high THC/high CBD (13.4 mg THC, 17.8 mg CBD) had the most significant improvement, with an increased pressure pain threshold. Interestingly, CBD-only preparations had no effect on pain [30].

A Cochrane review of drugs for fibromyalgia pain by Walitt et al. identified two studies which examined CBD in pain treatment, but these studies presented equivocal results [31]. No study provided high- to moderate-quality evidence for an outcome of efficacy, tolerability, and safety. Third-tier (very low quality) evidence indicated greater reduction of pain with cannabinoids, and study limitations of high disability levels and poor health-related quality of life (HRQoL) compared with placebo in another study. The authors found no convincing, unbiased, high-quality evidence suggesting that cannabinoids are of value in treating people with fibromyalgia [31].

Role in Headache

Baron et al. aimed to identify patterns of cannabis treatment in migraine and headache, as well as to analyze preferred cannabis strains. Of 2032 patients, 21 illnesses were treated with cannabis. Across all 21 illnesses, headache was a symptom treated with cannabis in 24.9% ($n = 505$) of which 88% ($n = 445$) of headaches were most likely migraine. Hybrid strains with a high THC/tetrahydrocannabinolic acid (THCA) and low CBD/cannabidiolic acid (CBDA) strain with β-caryophyllene followed by β-myrcene as the predominant terpenes were the most preferred by these patients for pain relief. This could reflect the potent analgesic, anti-inflammatory, and anti-emetic properties of THC. Moreover, many pain patients substituted prescription medications with cannabis, most commonly opiates/opioids, which may be due to the "opioid-sparing effect" of cannabinoids. These findings suggest the analgesic effect of medical cannabis in patients with headache and migraine [32]. Similarly, a retrospective, observational chart review by Rhyne et al. found that migraine headache frequency decreased significantly with medical marijuana use ($P < 0.0001$) [33]. Research suggests a role for medicinal cannabis in migraine headaches; however, there are no randomized controlled trials (RCTs) for validation and further evaluation.

Role in Visceral Pain

Cannabinoids have been piloted to address abdominal pain. However, a recent study showed no difference between THC and placebo in reducing pain [34]. The phase 2 RCT by De Vries et al. evaluated the analgesic efficacy, pharmacokinetics, safety, and tolerability of an oral tablet of THC in patients with chronic abdominal pain for ≥ 3 months after surgery or because of chronic pancreatitis. While no difference in pain reduction was found between the 65 patients receiving either THC or placebo, THC administered 3 times daily was safe and well tolerated during 50–52 days of treatment [34]. In

another study, De Vries et al. also assessed the analgesic efficacy, pharmacokinetics, tolerability, and safety of a single dose of THC in patients with chronic abdominal pain from chronic pancreatitis (CP). The randomized, single-dose, double-blinded, placebo-controlled, two-way crossover study subdivided 24 CP patients into opioid and non-opioid users. THC or active placebo was administered orally in a double dummy design. The study showed no treatment effect in reducing chronic abdominal pain from CP after a single dose of THC compared with placebo, but the THC was generally well tolerated [35].

Role in Postoperative Pain Management in Orthopedic Surgery

Hickernell et al. performed a retrospective cohort investigation to assess the efficacy of dronabinol (a synthetic cannabinoid, trade name Marinol), in addition to a standard multimodal pain regimen including opioids, on acute postoperative pain management following total hip and knee replacement. The 81 consecutive primary total joint arthroplasty (TJA) patients who received 5 mg of dronabinol twice daily in addition to a standard multimodal pain regimen were compared with a matched cohort of 162 TJA patients who received only the standard regimen. The dronabinol group had a shorter mean length of stay and consumed significantly fewer total opioid morphine equivalents versus the control group, but neither measure achieved statistical significance [36].

Role in Failed Back Surgery Syndrome

Failed back surgery syndrome (FBSS) is a spinal pain condition of unknown origin, either persisting despite surgical intervention or developing shortly after surgery in the same topographic location. Mondello et al. evaluated a combination of THC and CBD in association with spinal cord stimulation (SCS) in 11 FBSS patients diagnosed with neuropathic pain and suffering from moderate to severe chronic refractory pain. All patients discontinued previous unsuccessful therapy at least 2 months before starting THC/CBD therapy, except for the SCS, with both THC/CBD and SCS continued for 12 months. The results showed effective pain management as compared with baseline in all cases. Moreover, the positive effect of cannabinoid agonists on refractory pain was maintained during the entire duration of treatment with minimal dosage titration. The pain perception significantly decreased from baseline by the end of the study duration. The results indicated that cannabinoid agonists (THC/CBD) can have significant analgesic capabilities, for the treatment of chronic refractory pain in FBSS patients [37].

Cannabis and Opioids

There have been attempts made recently to find pharmaceutical alternatives to opioid treatment for chronic pain. Cannabinoids, when coadministered with opioids, may enable reduced opioid doses without loss of analgesic efficacy (i.e., an opioid-sparing effect). In a systematic review and meta-analysis on opioid-sparing effects of cannabinoids, 17 preclinical studies provided evidence of synergistic effects from opioid and cannabinoid coadministration [38•]. The meta-analysis of preclinical studies found that the median effective dose (ED50) of morphine administered in combination with THC was 3.6 times lower than the ED50 of morphine alone, and the ED50 for codeine in combination with THC was 9.5 times lower than the ED50 of codeine alone. One case series ($n = 3$) provided very-low-quality evidence of a reduction in opioid requirements with cannabinoid coadministration. Larger controlled clinical studies showed some clinical benefits of cannabinoids; however, opioid dose changes were rarely reported, and mixed findings were observed for analgesic benefit. In summary, preclinical studies provided robust evidence of the opioid-sparing effect of cannabinoids, whereas one of the nine clinical studies identified provided very-low-quality evidence of such an effect [38•].

Conclusion

Current research supports a potential role for medical cannabis in pain management, although effectiveness varies by individual and type of pain. As laws change regarding the use of cannabinoids in medicine, providers must become more comfortable discussing its appropriate uses in pain management. Interestingly, the opioid-sparing properties of medical cannabis make it an attractive option for pain management during this national opioid addiction crisis. However, the scale and quality of the studies conducted are limited. Further research including large RCTs are necessary to establish guidelines and treatment recommendations for medical cannabis in pain management, and proper patient education is essential.

Compliance with Ethical Standards

Conflict of Interest Amna Shaikh and Sarah Money declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodivers. 2007;4:1614–48.
2. •• Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in pain treatment: clinical and research considerations. J Pain. 2016;17:654–68 **This is a comprehensive review of cannabinoids, including an interesting history of its use, development and cultivation over time, and more current uses in medicine, as well as a physiologic review of its function.**
3. National Conference of State Legislatures. 2019. State medical marijuana laws. Available at http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (last accessed June 18, 2019). Google Scholar.
4. Bestrashniy J, Winters KC. Variability in medical marijuana laws in the United States. Psychol Addict Behav. 2015;29:639–42.
5. Light MK, Orens A, Lewandowski B, et al. Market size and demand for marijuana in Colorado. The Marijuana Policy Group. 2014. Available at www.colorado.gov/pacific/sites/default/files/Market%20Size%20and%20Demand%20Study,%20July%209,%202014%5B1%5D.pdf (last accessed November 17, 2016).
6. Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert ASB, Walton M, et al. Characteristics of adults seeking medical marijuana certification. Drug Alcohol Depend. 2013;132:654–9.
7. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain. 2018;19:37.
8. Sznitman SR, Bretteville-Jensen AL. Public opinion and medical cannabis policies: examining the role of underlying beliefs and national medical cannabis policies. Harm Reduct J. 2015;12:46.
9. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.
10. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365:61–5.
11. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346:561–4.
12. Alexander SP, Mathie A, Peters JA. Guide to receptors and channels (GRAC), 5th edition. Br J Pharmacol. 2011;164(Suppl 1):S1–324.
13. Hohmann AG, Herkenham M. Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. Neurosci Lett. 1998;252:13–6.
14. Hohmann AG, Herkenham M. Localization of central cannabinoid CB1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: a double-label in situ hybridization study. Neuroscience. 1999;90:923–31.
15. Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. Brain Res. 1999;822:17–25.
16. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9:254–64.
17. Kevin P. Hill, Matthew D. Palastro, Brian Johnson, and Joseph W. Ditre. Cannabis and cannabinoid research. Dec 2017.ahead of print https://doi.org/10.1089/can.2017.0017
18. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain. 2017;11(3):119–33.
19. Häuser W, Welsch P, Klose P, Radbruch L, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: a systematic review with meta-analysis of randomised controlled trials. Schmerz. 2019.
20. Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain Physician. 2017;20:E755–96 ISSN 2150–1149.
21. Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: prospective, observational study evaluating treatment in cancer patients on supportive or palliative care. Evid Based Complement Alternat Med. 2013;2013:510392.
22. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–49 ISSN 1526–5900.
23. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manag. 2013;46(2):207–18.
24. Kremer M. Antidepressants and gabapentinoids in neuropathic pain: mechanistic insights. Neuroscience. 2016;338:183–206.
25. Whiting PF, Wolff RF, Deshpande S, di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456–73.
26. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16:616–27.
27. Wilsey BL, Deutsch R, Samara E, et al. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. J Pain Res. 2016;9:587–98.
28. Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS One. 2011;6:e18440.
29. Calandre EP, Rico-Villademoros F, Slim M. An update on pharmacotherapy for the treatment of fibromyalgia. Expert Opin Pharmacother. 2015;16:1347–68.
30. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain. 2019;160(4):860–9.
31. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev 2016, Issue 7. Art. No.: CD011694.
32. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain. 2018;19:37.
33. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of medical marijuana on migraine headache frequency in an adult population. Pharmacotherapy. 2016;36:505–10.
34. de Vries M, et al. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase placebo-controlled study. Clin Gastroenterol Hepatol. 2017;15(7):1079–1086.e4.
35. de Vries M, Van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, Van Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. Br J Clin Pharmacol. 2016;81(3):525–37.
36. Hickernell TR, Lakra A, Berg A, Cooper HJ, Geller JA, Shah RP. Should cannabinoids be added to multimodal pain regimens after

total hip and knee arthroplasty? J Arthroplast. 2018;33(12):3637–41. https://doi.org/10.1016/j.arth.2018.07.027. Epub 2018 Aug 3.

37. Mondello E, Quattrone D, Cardia L, Bova G, Mallamace R, Barbagallo AA, et al. Cannabinoids and spinal cord stimulation for the treatment of failed back surgery syndrome refractory pain. J Pain Res. 2018;11:1761–7 Published 2018 Sep 6.

38.• Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, Lintzeris N, Khor KE, Farrell M, Smith A, le Foll B Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacology. 2017;42(9):1752–1765. doi:https://doi.org/10.1038/npp.2017.51. **This review examines the potential of cannabinoids to reduce opioid burden and provides a review of available studies with calculated opioid dose reduction.**