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CANNABIS FOR MEDICAL PURPOSES EVIDENCE GUIDE

Information for Pharmacists and
Other Health Care Professionals

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MEDICAL CANNABIS

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Introduction

This evidence guide was prepared to provide pharmacists and other health care providers with a curated summary of the best available evidence of the use of medical cannabis and cannabinoids for a variety of indications, including pain, multiple sclerosis (MS), chemotherapy-induced nausea/vomiting (CINV), and epilepsy.

While there are a number of trials of variable quality investigating the use of cannabis for medical purposes, there is a paucity of robust evidence in this area. References selected for this guide include key systematic reviews, meta-analyses and randomized control trials. Guidelines reporting the quality of evidence for their recommendation and adverse effects were also included. Studies based on case reports, anecdotal evidence, expert opinions and those with weak design were excluded from this summary. Even so, current best available evidence is of moderate quality, and limitations include lack of standardized measure for pain across the pain studies, short duration of the studies and challenges with blinding and creating a placebo control.

Finally, the majority of these studies look at the use of cannabis in the context of third or fourth line adjunctive therapy and they do not support the use of cannabis in place of standard therapies for any indication. Research into the medical uses of cannabis and cannabinoids is constantly evolving and this document will be updated regularly to align with the most current evidence.

LIBRARY OF REFERENCES

General Pain

Whiting P, Wolff R, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*. 2015; 313(24):2456-73. doi: 10.1001/jama.2015.6358.

Objective: Systematic review of the benefits and adverse events of cannabinoids.

Methods: Twenty-eight pain studies: 12 on neuropathic pain (central, peripheral or not specified), 3 on cancer, 3 on diabetic peripheral neuropathy, 2 on fibromyalgia, 2 on HIV-associated sensory neuropathy and 1 on each of MS refractory pain, rheumatoid arthritis (RA), non-cancer pain, central pain, musculoskeletal and chemotherapy-induced pain. Cannabinoids were administered in addition to standard therapy: 13 studies used nabiximols, 4 used smoked THC, 5 used nabilone, 3 used THC oromucosal spray, 2 used dronabinol, 1 used vaporized cannabis, 1 used oral THC and 1 used ajuvenic acid capsules.

Results: The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo in cancer and neuropathic pain (OR, 1.41 [95%CI, 0.99-2.00]; 8 trials). One smoked THC trial reported greatest beneficial effect (OR, 3.43 [95%CI, 1.03-11.48]).

Conclusion: Paper concluded that there was moderate-quality evidence based on the GRADE approach to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic pain or cancer pain (smoked THC and nabiximols).

Limitations: Included trials had a number of weaknesses such as failure to appropriately handle withdrawals, selective outcome reporting, inadequate description of methods of randomization, allocation concealment and blinding. The included studies used various measures to evaluate similar outcomes, different types of cannabinoids were used and different routes of administration.

Acute Pain

Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. *Acta Anaesthesiol Scand*. 2017;61(3):268-80. doi: 10.1111/aas.12851.

Objective: Assess the analgesic efficacy and adverse effects of cannabinoids when used for the management of acute pain.

Methods: Seven randomized control trials (RCTs) assessing analgesic efficacy of cannabinoids compared to placebo or active comparator with a total of 611 patients.

Results: Five studies found cannabinoids equivalent to placebo, 1 found cannabinoids superior to placebo and 1 found cannabinoids inferior to placebo.

Strength of Evidence: Strength of the body of the evidence was assessed using GRADE method: Moderate quality evidence.

Conclusion: Studies failed to demonstrate cannabinoid efficacy in acute pain. Paper concluded that cannabinoids don't play a role in acute pain management.

Limitations: The risk of bias was unclear for a high proportion of the assessments due to inadequate description of their methodologies. The studies had different comparator drugs, clinical models of acute pain, populations, methods of reporting and assessing pain and different cannabinoid medications. Only 7 RCTs were included.

Cancer Pain

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. doi: 10.1016/j.jpain.2012.01.003.

Objective: Investigate safety and efficacy of nabiximols compared to placebo in poorly-controlled cancer pain.

Methods: Three-hundred-and-sixty patients with advanced cancer and opioid-refractory pain received placebo or nabiximols (2.7mg THC, 2.5mg CBD) at low dose (1-4 sprays/day), medium dose (6-10 sprays/day) or high dose (11-16 sprays/day). Average pain, worst pain and sleep disruption were measured daily during 5 weeks of treatment; 263 patients completed the study.

Results: Thirty percent responder rate primary analysis was not significant for nabiximols vs placebo ($p = 0.59$). Significantly greater response to nabiximols vs placebo ($p = 0.035$) in secondary continuous responder analysis of average daily pain from baseline to end of study especially at low dose ($p = 0.008$) and medium dose ($p = 0.039$).

Conclusion: This study supports the efficacy and safety of nabiximols at the 2 lower-dose levels and provides important dose information for future trials.

Limitations: Doses were not individualized based on patients' conditions. Changes in opioid dosing was discouraged to simplify data analysis, but this reduced the ability to discern opioid-sparing potential of cannabinoids.

Neuropathic Pain

Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple-sclerosis-related pain. *Curr Med Res Opin*. 2007;23(1):17-24. doi: 10.1185/030079906X158066.

Objective: Summarize efficacy and safety data of cannabinoid-based drugs for neuropathic pain.

Methods: Seven articles were included with total of 298 patients. Data included baseline and endpoint pain scores on a 10cm long visual analog scale (VAS) or 11-point ordinal scale.

Results: Data of all cannabinoids pooled together resulted in decrease in pain scores of 1.6 ± 0.4 points ($p < 0.001$). At endpoint cannabinoids were superior to placebo by 0.8 ± 0.3 points ($p = 0.029$).

Strength of Evidence: Jadad criteria. All of the papers scored "good" (5 scored max of 5 points, 1 scored 4, the others scored 3. Average = 4.6 points).

Conclusion: Cannabinoids including buccal spray are effective in treating neuropathic pain in MS.

Limitations: Study was based on the assumption that MS pain is similar to other neuropathic pain. No studies examined a duration of treatment longer than 6 weeks. Different types of cannabinoids were used in the studies (CBD/THC buccal spray, CBD, and dronabinol).

Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective cannabinoids for chronic neuropathic pain: A systematic review and meta-analysis. *Anesth Analg*. 2017;125(5):1638-52. doi: 10.1213/ANE.0000000000002110.

Objective: Determine the analgesic efficacy and safety of selective cannabinoids.

Methods: Eleven RCTs comparing selective cannabinoids (dronabinol, nabilone, nabiximols) to conventional treatments or placebo. Studies included 1219 patients, ≥18 years old with neuropathic pain for at least 3 months of moderate or severe pain intensity.

Results: Treatment group reported significant, but clinically small, reduction in mean numerical rating scale pain scores (0-10 scale) vs comparator (-0.65 points; 95%CI, -1.06 to -0.23 points; P = 0.002).

Strength of Evidence: Certainty of evidence classified using GRADE approach. GRADE: weak recommendation and moderate-quality evidence.

Conclusion: Selective cannabinoids provide small analgesic benefit in patients with chronic neuropathic pain.

Limitations: There was variability in quality of reporting, etiology of neuropathic pain, type and dose of selective cannabinoids.

Andreae MH, George MH, Naum S, et al. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *The Journal of Pain*. 2015; 16 (12): 1221-32. doi: 10.1016/j.jpain.2015.07.009.

Objective: Synthesize the evidence on the use of inhaled cannabis for chronic neuropathic pain.

Methods: Included 5 RCTs with total 178 patients for a duration of up to 2 weeks. Studies compared inhaled cannabis (whole cannabis plant) administered as pre-rolled cigarettes, volcano vaporizer (1 study) or gel capsule inhaled through pipe (1 study) to placebo.

Results: Odds ratio for ≥30% reduction in pain scores with cannabis vs placebo was 3.2 (Bayesian 95% CRI [1.59, 7.24]) which is at least moderate benefit as defined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).

Conclusion: Paper suggests that inhaled cannabis provides short-term benefits for 1 in 5 to 6 patients with chronic neuropathic pain.

Limitations: Studies had different etiologies of neuropathic pain. The paper included a small number of studies, small patient sample size, attrition of patients and short duration. Bias may have occurred due to ineffective patient blinding.

Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic non-cancer pain: Systematic review of randomized control trials. *Can Fam Physician*. 2015;61(8):e372-81. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4541447>. Published: August 2015. Accessed: January 2018.

Objective: Determine if medical marijuana provides pain relief for patients with chronic non-cancer pain (CNCP) and determine the therapeutic dose, adverse effects and specific indications.

Methods: Six RCTs studying smoked or vaporized cannabinoids (non-synthetic). Five of the studies were on neuropathic pain (adjunct to other concomitant analgesic). Duration of intervention period was maximum of 5 days. Duration of the trials ranged between 17 days and 8 weeks.

Conclusion: There was evidence for using low-dose medical marijuana in refractory neuropathic pain and traditional analgesics. This study doesn't support generalized use of medical marijuana for all CNCP.

Limitations: Studies included were of short duration and only 6 studies were included. There was variable etiology of neuropathic pain and patients had variable previous experience with cannabis. Studies that allowed patients to use concurrent analgesics didn't report the baseline dose.

Multiple Sclerosis Pain

Jawahar R, Oh U, Yang S, Lapane K. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs*. 2013;73(15):1711-22. doi: 10.1007/s40265-013-0125-0.

Objective: Systematically review pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients.

Methods: Included 15 studies of lengths varying between 5 and 14 weeks. Studies investigated nabiximols (2.7mg Δ -9-THC and 2.5mg CBD oromucosal spray) and dronabinol (2.5mg oral THC capsule).

Results: A Class I trial on nabiximols in participants experiencing central pain reported improvement in pain scores. Another class I trial on nabiximols (on spasticity, spasms, bladder problems, tremor, and/or non-musculoskeletal pain) reported no improvement in pain. The Class 3 trial on dronabinol reported improvement in pain scores for participants with central pain. The pooled effect size for cannabinoids (3 studies, 565 participants) was 0.08 (95% CI: -0.74 to 0.89).

Conclusion: This meta-analysis doesn't support the use of nabiximols in pain reduction.

Limitations: Only 3 of the 15 included studies examined THC/CBD. Studies had poor quality of reporting on allocation concealment and compliance in treatment and comparison groups.

Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ*. 2010;182(14):E694-701. doi: 10.1503/cmaj.091414.

Objective: To further explore the safety and efficacy of smoked cannabis in 23 adults with post-traumatic or post-surgical neuropathic pain.

Method: Investigated smoked cannabis (0%, 2.5%, 6%, 9.4% THC). Inhale single 25mg dose through pipe TID for 5 days, then a 9-day washout period over four 14-day periods. Average intensity measured using 11-point numeric rating scale.

Results: Average daily pain intensity lower on 9.4% THC vs 0% THC (5.4 vs 6.1; difference = 0.7, 95% CI 0.02-1.4); 9.4% THC reported improved ability to fall asleep (easier, $p = 0.001$; faster $p < 0.001$, more drowsy $p = 0.003$) and improved quality of sleep ($p = 0.01$) compared to 0% THC.

Conclusion: Single inhalation of 25mg of 9.4% THC herbal cannabis TID reduced intensity of pain, improved sleep and was well tolerated.

Limitations: Only 23 patients were included. Duration of treatment was only 5 days. The maximum THC content was based on the legal limit rather than titration to effective dose. Potential for carryover effect due to short washout period.

Spasticity in Multiple Sclerosis

Whiting P, Wolff R, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358.

Objective: Systematic review of the benefits and adverse events of cannabinoids.

Methods: Fourteen studies on spasticity due to MS (11) or paraplegia (3) investigating cannabinoids vs placebo. Six studies assessed nabiximols, 3 dronabinol, 1 nabilone, 4 THC/CBD and 1 each for ECP002A and smoked THC.

Results: Mean decrease of 0.12 points in the Ashworth score in cannabinoids vs placebo (WMD, -0.12 [95%CI, -0.24 to 0.01]; 5 trials), which is not a significant difference. Cannabinoids also associated with greater average improvement using numerical rating scales (mean difference, -0.76 [95%CI, -1.38 to -0.14]; 3 trials). Average number of patients reporting an improvement on global impression of change score was greater with nabiximols vs placebo (OR 1.44 [95%CI, 1.07 to 1.94]; 3 trials).

Conclusion: Based on the GRADE approach there was moderate-quality evidence to support the use of cannabinoids in spasticity due to MS.

Limitations: Included trials had a number of weaknesses such as failure to appropriately handle withdrawals, selective outcome reporting, inadequate description of methods of randomization, allocation concealment, and blinding. The included studies used various measures to evaluate similar outcomes, different types of cannabinoids were used and different routes of administration. There are concerns about the reliability of the modified Ashworth spasticity scale.

Corey-Bloom J, Wolfson T, Jin S, Marcotte T, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ*. 2012; 184(10):1143-50. doi: 10.1503/cmaj.110837.

Objective: Determine short-term effect of smoked cannabis on spasticity in MS.

Methods: Study included 37 adult patients with MS and spasticity. The intervention was smoked cannabis (once daily for 3 days) compared to identical placebo cigarettes.

Results: Smoking cannabis resulted in reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$). Pain scores on a visual analogue scale were reduced by average 5.28 points more than with placebo ($p = 0.008$). There was no change in timed walk and no serious adverse effects. The results of this paper were also discussed in the systematic review by Whiting et al.

Conclusion: Smoked cannabis was superior to placebo in symptom and pain reduction in treatment-resistant spasticity.

Limitations: Intervention duration was only 3 days. Many patients had previous experience with cannabis and recognized the positive response to cannabis. There are concerns about the reliability of the modified Ashworth spasticity scale.

Zajicek J, Hobart J, Slade A, Barnes D, Mattison P. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012;83(11):1125-32. doi: 10.1136/jnnp-2012-302468.

Objective: Report the results of the MS and Extract of Cannabis (MUSEC) study that aimed to substantiate the patient-based findings of previous studies.

Methods: Double-blind phase III, RCT of 279 patients with stable MS at 22 UK centers and a treatment duration of 12 weeks with oral cannabis extract (CE) or placebo.

Results: Proportion of patients with self-reported relief was 29.4% in the cannabis group and 15.7% in the placebo group (OR 2.26, 95%CI 1.24 to 4.13, $p = 0.004$, one sided). Self-reported relief from muscle stiffness was consistently higher with CE than placebo. Difference was significant ($p < 0.025$, one sided). The results of this paper were also discussed in the systematic review by Whiting et al.

Conclusion: Study demonstrated the superiority of CE over placebo in the treatment of muscle stiffness in MS.

Limitations: There was no objective measure of spasticity. Subjective rating scales were used and, as with all rating scales, a patient's self-rated score may be influenced by their condition at the time of response

Meza R, Pena J, Garcia K, Corsi O, Rada G. Are cannabinoids effective in multiple sclerosis? *Medwave*. 2017; 17(Suppl1):e6865. doi: 10.5867/medwave.2017.6865.

Objective: Investigate the role of cannabinoids in MS.

Methods: Meta-analysis of 25 systematic reviews was conducted to summarize findings using GRADE approach. One study was on smoked cannabis, 9 on cannabis capsules, 2 on dronabinol, 10 on SL nabiximols spray and others on less conventional methods.

Results: Cannabinoids do not reduce spasticity in MS. The certainty of the evidence is high. Cannabinoids do not reduce pain in MS. The certainty of the evidence is high. Cannabinoids are associated with adverse effects, which are probably frequent in MS. The certainty of the evidence is moderate.

Conclusion: Cannabinoids do not reduce spasticity or pain in multiple sclerosis and they are associated with adverse effects which are probably frequent in MS.

Limitations: There was variability in the route of administration and the type of cannabinoids used. Not all of the trials reported the severity of the disease of the patients. Only 7 randomized trials reported the effects of cannabinoids on pain and spasticity in MS and were included in the meta-analysis.

Chemotherapy-Induced Nausea/Vomiting (CINV)

Whiting P, Wolff R, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358.

Objective: Systematic review of the benefits and adverse events of cannabinoids.

Methods: Cannabinoids were administered in addition to standard therapy; 28 trials were conducted on nausea and vomiting. Fourteen studies were on nabilone, 3 on dronabinol, 1 on Nabiximols, 4 on levonantradol and 6 on THC.

Results: All suggested greater benefit of cannabinoids vs active comparators and placebo (not all were statistically significant). Greater number of patients showed complete nausea and vomiting response with cannabinoids vs placebo (OR, 3.82 [95% CI, 1.55-9.42]; 3 trials).

Conclusion: There was low quality evidence suggesting that cannabinoids were associated with improvement in CINV.

Limitations: Included trials had a number of weaknesses such as failure to appropriately handle withdrawals, selective outcome reporting, inadequate description of methods of randomization, allocation concealment, and blinding. The included studies used different types of cannabinoids and different routes of administration.

Epilepsy

Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376(21):2011-20. doi: 10.1056/NEJMoa1611618.

Objective: Study cannabidiol (CBD) for the treatment of drug-resistant seizures in the Dravet Syndrome.

Methods: One-hundred-and-twenty children and young adults with Dravet Syndrome and drug-resistant seizures were included. CBD oral solution (dose of 20mg per kilogram of body weight/day) was administered in addition to standard antiepileptic treatment and compared to placebo over a 14-week treatment period compared to a 4-week baseline period.

Results: Significant decrease in median frequency of convulsive seizures per month (from 12.4 to 5.9 with CBD vs from 14.9 to 14.1 with placebo [95%CI, -41.1 to -5.4; p = 0.01]). Patients' overall condition improved by at least 1 category on seven-category Caregiver Global Impression of Change scale in 62% of the CBD group vs 34% of the placebo group (P = 0.02). No significant reduction in non-convulsive seizures. Adverse events occurred more frequently in the CBD group such as diarrhea, vomiting, fatigue, pyrexia, somnolence and abnormal results on liver-function tests.

Conclusion: CBD resulted in greater reduction in frequency of convulsive-seizures. It was also associated with more adverse effects.

Limitations: Potential unblinding of patients due to recognition of adverse effects and unpalatability of the active treatment.

Thiele E, Marsh E, French J, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*.2018;S0140-6736(18): 30136-3. doi: 10.1016/S0140-6736(18)30136-3.

Objective: Assess the efficacy and safety of CBD as an add-on anticonvulsant therapy in patients with Lennox-Gastaut syndrome.

Methods: Double-blind RCT at 24 clinical sites with a total of 171 patients. Patients were randomly assigned to receive 20mg/kg oral CBD daily or matched placebo for 14 weeks.

Results: Median percentage reduction in monthly drop seizure frequency from baseline was 43.9% (IQR -69.6 to -1.9) in CBD group vs 21.8% (IQR -45.7 to 1.7) in placebo group. Estimated median difference between treatment groups was -17.21 (95% CI -30.32 to -4.09; p = 0.0135). Adverse events occurred in 74 (86%) patients in CBD group and 59 (69%) patients in placebo group; most were mild or moderate.

Conclusion: Add-on CBD is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated.

Limitations: CBD was used as add-on therapy to conventional antiepileptic drugs which requires evaluation of potential drug-drug interactions. Only a single dose of CBD was used and thus dose-response effects can't be determined. There was poor ethnic diversity (90% of patients were white). Long-term CBD efficacy and safety data are needed.

Guidelines

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. <https://www.nap.edu/resource/24625/Cannabis-conclusions.pdf>. Published: January 2017. Accessed: January 18, 2018.

Content: Includes indications for the use of cannabis and the level of evidence available for each conclusion. It also includes recommendations outlining research approaches and objectives that are priority for research.

College of Family Physicians of Canada. Authorizing Dried Cannabis for Chronic Pain or Anxiety: Preliminary Guidance from the College of Family Physicians of Canada. Mississauga, ON: College of Family Physicians of Canada; 2014. https://www.cfpc.ca/uploadedFiles/Resources/_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf. Published: September 2014. Accessed: January 19, 2018.

Content: Includes the minimum recommended age for use of cannabis, recommendations on safe-use, dosing, harm prevention, and assessment monitoring and communication with patients and consultants. Resources such as calculations for dosing and tools for screening patients for misuse or addiction risk are also included. The recommendations were also graded levels I-III based on the quality of evidence available.

Royal Australian College of General Practitioners. Medicinal use of cannabis products: RACGP Position Statement. <https://www.racgp.org.au/download/Documents/Policies/Clinical/RACGP-position-on-medical-cannabis.pdf>. Published: October 2016. Accessed: January 19, 2018.

Content: Includes indications for the use of cannabis with the GRADE level of evidence for each condition and the short-term adverse effects associated with each cannabinoids type. It also lists the different conditions and the GRADE level of evidence for cannabinoids efficacy in those conditions.

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