

Topical Cannabinoids for Treating Chemotherapy-Induced Neuropathy: A Case Series

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Abstract

Background: Chemotherapy-induced peripheral neuropathy is a common and often severe side effect from many chemotherapeutic agents, with limited treatment options. There is no literature on the use of topical cannabinoids for chemotherapy-induced neuropathy. **Case Presentations:** The current manuscript presents a case series of patients presenting in oncology clinics at Sutter Health, CA and Mayo Clinic, Rochester, MN from April 2019 to December 2020 with chemotherapy-induced peripheral neuropathy who used topical creams containing the cannabinoids delta-nine-tetrahydrocannabinol (THC) and/or cannabidiol (CBD). **Conclusions:** This case series suggests that topical cannabinoids may be helpful for patients with chemotherapy-induced peripheral neuropathy. This paper also discusses the potential mechanisms of action by which topical cannabinoids might alleviate established CIPN symptoms. A randomized placebo-controlled trial using a standardized product is planned to study the actual efficacy of such treatment.

Keywords

cannabinoids, chemotherapy-induced peripheral neuropathy, topicals, CBD

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose- and age-dependent side effect associated with 6 main antitumor agent drug classes: platinum-based drugs (eg, oxaliplatin), taxanes (eg, paclitaxel and docetaxel), vinca alkaloids (eg, vincristine), epothilones (eg, ixabepilone), proteasome inhibitors (eg, bortezomib), and immunomodulatory drugs (eg, thalidomide).¹ In a review of over 30 clinical studies, CIPN prevalence was reported to be approximately 68% when measured in the first month after finishing a variety of chemotherapy agents, most of which had been associated with CIPN; it was 60% at 3 months and 30% (6.4–53.5) at 6 months or more.²

CIPN remains a challenge to treat, as most agents used in practice, such as tricyclic antidepressants, anticonvulsants (gabapentin and pregabalin), or serotonin-norepinephrine reuptake inhibitors (SNRI, primarily duloxetine) provide limited benefit to most patients and can have significant side effects.^{3–5}

The mechanism of CIPN broadly includes the production of neuronal toxicity and inflammation.⁶ The 6 main

classes of antitumor agents, discussed above, cause damage to peripheral sensory, motor, and autonomic neurons, through such mechanisms as microtubule disruption, DNA damage, altered ion channel activity, myelin sheath damage, oxidative stress, and mitochondrial damage.⁷ In addition, the cumulative damage leading to increased activation of the immune system ultimately promotes cell damage and death in peripheral neurons, leading to a sensitization to nociceptive responses.⁶ The central nervous system may also play a role in CIPN by a number of mechanisms, including hyperactivity, reduced GABAergic inhibition, neuroinflammation, and overactivation of GPCR/MAPK pathways^{8–10}

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The cannabinoids delta-nine-tetrahydrocannabinol (THC) and cannabidiol (CBD) have shown some mild efficacy in the treatment of pain,^{11,12} including neuropathic pain.^{3,13-20} However, not all studies have been positive; Lynch et al²¹ reported in a small pilot RCT no overall benefit from nabiximol oral mucosal spray but noted that 5/18 patients were responders and concluded that a larger RCT is warranted.

Cannabinoids may exert their effects through peripheral and/or central mechanisms, as targets for action are present in both. THC interacts with the endocannabinoid system primarily through the activation of cannabinoid 1 (CB₁) and cannabinoid 2 (CB₂) receptors.²² CBD does not interact efficiently to activate known cannabinoid (CB₁ and CB₂) receptors.²³ CBD, however, can antagonize the activity of CB₁ and CB₂ receptor agonists.²⁴ As a result of not activating CB₁ receptors, CBD does not produce the psychoactivity that is typically associated with other cannabinoid agonists. Indeed, recent evidence suggests that CBD may reduce the untoward effects of psychoactive cannabinoids, including cognitive impairment, anxiety, and paranoia.²⁵

THC and additional CB₁ and CB₂ receptor agonists have been shown to be effective at reducing CIPN in multiple preclinical models.^{6,26} THC and additional cannabinoids, through CB₁ and/or CB₂ receptors, have the potential to modulate pain through a variety of mechanisms, including inhibition of calcium channel activity, transient receptor potential (TRP) channels, serotonin, GABA and glutamate receptor signaling, and modulation of the immune system, leading to anti-inflammatory activity.²⁷⁻²⁹ Inhaled cannabis has also been reported to be effective for treating HIV-associated neuropathy, possibly via CB₁ agonism.¹⁵

CBD has been shown to be a molecule with pleiotropic effects that ultimately leads to reduction in oxidative stress and inflammation.³⁰ Increasingly, preclinical evidence demonstrates that CBD has anti-neuropathic pain effects in multiple rodent models, including models of CIPN.³⁰⁻³⁴ Interestingly, there is significant overlap with mechanisms controlling pain when CBD and THC are compared. CBD has been shown to inhibit pain through modulation of calcium and TRP channels, serotonin receptors, glycine receptors, and modulation of the immune system⁶ microglia and macrophage function,³⁵ leading to anti-inflammatory activity.

Cannabis is being used by at least 20% to 30% of cancer patients for pain, nausea, insomnia, and other cancer related issues.³⁶⁻⁴⁰ More research is desperately needed, noting that cannabis as an adjunct for supportive care is promising given the lack of serious adverse events and/or known interactions with chemotherapy.³⁶ Given that many patients do not have access to systemic *Cannabis*, and/or want to avoid the psychoactive effects of THC, a more local means of providing cannabinoids might be preferable. Cannabinoids happen to be lipophilic agents and, thus, can permeate skin.^{41,42} Taking advantage of this delivery technique, a small pilot clinical trial evaluated a topical cannabinoid

cream, reporting data that supported that it improved non-chemotherapy induced neuropathic pain.⁴³ The current report involves a case series of patient experiences using topical cannabis products for painful CIPN symptoms.

Methods

This is an informal case series obtained by interviewing patients in an oncology clinic who were using topical cannabis for CIPN symptoms from April 2019 to December 2020 at Sutter Medical Group, Sacramento CA and Mayo Clinic, Rochester, MN. Patients with CIPN were reporting that they were using topical cannabis for established painful CIPN. Due to this novel approach, patients with a history of painful CIPN seen in the oncology clinic were asked if they had tried topical cannabis for CIPN, and if so, what was their response. Patients were specifically asked by the authors about the type of product, duration of response, and any side effects. Charts were retrospectively reviewed to look at other prior treatments for neuropathy, prior chemotherapy, and type of cancer.

This case series was approved by the Sutter Health Expedited Review Committee, San Francisco, CA, May 14, 2020. Written consent for publication was obtained by the author from the patients with detailed case reports and is located in the patient medical record.

Results

Patients were obtaining topical products from retail stores (containing hemp-derived CBD) or cannabis dispensaries (containing either CBD alone or CBD and THC). In some cases, creams containing only CBD were derived from hemp; in general, retail obtained hemp contains 0.3% or less of THC.⁴⁴ The creams used contained between 120-600 mg per unit (tube or jar) of CBD and 6-600 mg THC per unit. Some of the creams contain ingredients that are reported to increase skin absorption, such as essential oils or emu oils.^{45,46} Some of these patients had tried other agents/acupuncture with little or no benefit but reported improvement in pain/burning or tingling sensations after starting topical cannabinoids. However, all patients that reported benefit had neuropathy symptoms return after several hours, suggesting that the benefit is transient. Only 1 patient reported side effects, specifically transient worsening of neuropathy that returned to baseline after discontinuing the topical. Table 1 describes patients that reported benefits from using topical cannabis, and Table 2 describes patients that did not have any benefit.

Sample Case Studies Demonstrating Responses to Treatments With a Topical Cream Containing CBD or CBD/THC

Case 1: 49-year-old male with myeloma, treated with chemotherapy in 2008 (lenalidomide, bortezomib, dexamethasone)

Table 1. Patients Reporting Benefit From Topical Cannabis.

Pt	Cancer type	Chemotherapy	Location of symptoms	Treatments tried/failed	Cannabis type
1	Myeloma	RVD/transplant	Feet	Duloxetine, Gabapentin, pregabalin, acupuncture	CBD
2	Breast	AC-T	Feet	Gabapentin	CBD/THC
3	Pancreatic	FOLFOXIRI	Hands/feet		CBD/THC
4	Primary peritoneal	Taxol/carbo	Feet		CBD
5	Breast	Capecitabine/eribulin	Feet		THC/CBD
6	Lymphoma	R-CVAD	Hands/feet		CBD
7	Breast	AC-T	Feet	Gabapentin	CBD
8	Breast	AC-T	Feet, legs		CBD/THC
9	Ovarian	Paclitaxel/carboplatin /bevacizumab	Feet		CBD
10	Breast	AC-T	Feet	Acupuncture	CBD
11	Uterine	Paclitaxel	Hands		THC/CBD
12	Colorectal	FOLFOX	Hands/feet	Gabapentin	CBD/THC
13	Ovarian	Paclitaxel/carboplatin	Hands/feet	Gabapentin	CBD/THC
14	Pancreas	FOLFOX	Feet		CBD
15	Pancreas	FOLFOX	Hands		CBD/THC
16	Breast	Paclitaxel/carboplatin	Feet		CBD/THC
17	Ovarian	Paclitaxel/carboplatin	Hands/feet	Gabapentin	CBD
18	Breast	TC	Hands		CBD
19	Primary peritoneal cancer	Paclitaxel/carboplatin	Feet		CBD
20	Breast	AC-T	Hands/feet	Duloxetine, acupuncture, hydrotherapy	CBD
21	Pancreatic	FOLFOXIRI	Feet		CBD
22	Ovarian	Taxol	Hands/feet		CBD/THC

Table 2. Patients Who Tried Topical Cannabis Products and Did Not Report Any Benefit.

Pt	Cancer type	Chemotherapy	Location of symptoms	Treatments tried/failed	Cannabis type
1	Bladder	Carbo/Gem; cisplatin	Feet		CBD
2	Prostate	Docetaxel	Feet		CBD
3	Breast	AC-T	Feet	SSRI, gabapentin, acupuncture	CBD/THC
4	Breast	AC-T	Hands/feet		CBD

Abbreviations: RVD, lenalidomide/bortezomib/dexamethasone; AC-T, doxorubicin, cyclophosphamide/paclitaxel; TC, docetaxel and cyclophosphamide; FOLFOXIRI, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin

followed by autologous bone marrow transplant. He developed severe neuropathy in his feet that limited his activities. He had tried gabapentin, pregabalin and duloxetine, without any benefit. He started acupuncture in 2019, which also was not beneficial. He had been using oral cannabis for years for arthritis pains/sleep, but it had no effect on his CIPN. He started using a CBD cream (250mg/jar) 1 to 2 times per day and reported significant improvement in his neuropathic pain. This cream contains essential oils and ingredients that may enhance skin penetration.⁴⁸ He rated his baseline pain at 7 to 10 which diminished to 4-5/10 within 5 minutes of application; he noted that the effect lasted throughout the night. He noted a slight feeling on heat upon application but no pain or other adverse effects.

Case 2: 73-year-old female with breast cancer, treated with doxorubicin, cyclophosphamide, and paclitaxel (AC-T) for stage II breast cancer in 2017. She developed neuropathy in her feet that was bothersome at night. She had tried gabapentin, without benefit, and developed dizziness from it. She started a THC/CBD cream (unknown mg), obtained from local cannabis dispensary. This cream contains emu oil which has been shown to increase skin absorption.⁴⁹ Baseline neuropathy was rated at 8/10 which improved to 2-3/10, within minutes after application. She reported that the benefit lasted throughout the night with no adverse effects. She stopped gabapentin and continued to use the cannabis cream with ongoing benefit.

Case 3: 65-year-old male with pancreatic cancer who developed CIPN after oxaliplatin-based chemotherapy. His baseline neuropathy was rated as 6/10 in his feet and hands. He reported using an artisan cream containing approximately 600 mg CBD, 600 mg THC per jar. This cream also contained essential oils to aid in absorption.⁴⁸ His symptoms improved to 4/10 after application within a few days and benefits last most of the day. He continues to use the cream daily with no adverse effects.

Case 4: 71-year-old female with primary peritoneal cancer who developed painful CIPN after taxane-based chemotherapy, rated at 7/10. She reported using a CBD cream (250 mg/jar) that reduced pain to 3/10 within minutes and lasts about 12 hours. This cream contains essential oils and other ingredients to enhance skin absorption. She uses the cream daily with no side effects.

Case 5: 78-year-old female with advanced breast cancer who developed CIPN after capecitabine-eribulin chemotherapy. Baseline CIPN, rated at 6/10, reduced to 1/10 in feet after 15 minutes of applying a cream with CBD 180 mg/THC 6 mg per jar. She reports the benefit lasts 24 hours and she uses it daily with no reported side effects.

Case 6: 59-year-old male with lymphoma who developed severe CIPN in his feet and hands after receiving cyclophosphamide, vincristine, doxorubicin, and dexamethasone, rating his pain at 10/10 baseline. He uses a cream with 200 mg/jar CBD only and reports improvement to 5/10 after about 30 minutes. The effect lasts about 3 hours, without any side effects.

Case 7: 60-year-old female with breast cancer, who developed CIPN after AC-T chemotherapy, rated 8/10 at night in feet despite gabapentin. She uses a CBD cream (120 mg/jar) and notes improvement to 0/10 within 10 to 15 minutes, with the benefit lasting through the night. This cream contains essential oils to enhance absorption. She uses the cream nightly and reports no side effects.

Case 8: 55-year-old female who developed CIPN in her feet and legs after AC-T chemotherapy for breast cancer. Baseline CIPN rated at 6/10 which improved to 1/10 using a cream containing 477 mg THC and 158 mg CBD/jar. Noted improvement in 10 to 15 minutes and effect lasts 2 to 3 hours. She is using the cream a few times a week, mostly at night which helps with sleep with no side effects.

Case 9: 64-year-old female with recurrent ovarian cancer, developed painful CIPN after taxane-based chemotherapy. Baseline pain was rated at 6/10 in feet, improved to 4/10 after using CBD oil (250 mg/jar). She notes the oil starts to work in 10 minutes, with effect lasting through the night. She uses nightly, sometimes applies in the morning, as well, with no reported side effects.

Case 10: 62-year-old female with breast cancer who developed neuropathy due to AC-T chemotherapy in feet. She tried acupuncture without any benefit. Rated baseline neuropathy at 8/10 which improved to 5/10 after using CBD

cream (unknown mg) after 10 minutes, with effect lasting about 3 hours. She is using the cream BID with no side effects.

The above 10 cases are summarized as the first ten cases in Table 1, followed by 12 additional case summaries.

Discussion

The positive results reported by patients in this case series are consistent with the current literature that cannabis products can decrease neuropathic pain in people, from a variety of conditions, including CIPN. Most of the patients reporting benefit described a partial decrease in painful CIPN symptoms with the onset of perceived benefit in about 10 to 15 minutes; this benefit generally lasted a few hours up to 24 hours. However, a minority of patients using topical products did not report any benefit. Only 1 patient reported a side effect, that being transient worsening of neuropathic pain: this patient discontinued use of the cream.

There are multiple preclinical models to suggest mechanisms by which cannabinoids may help alleviate CIPN. In rodent models of CIPN, a decrease of endocannabinoid levels has been observed, suggesting activation of the system may provide benefit.⁴⁷⁻⁴⁹ Indeed, THC and additional CB₁ and CB₂ receptor agonist, or modulators of the endocannabinoid system, have been shown to suppress neuropathic pain, by several different mechanisms,²⁹ including in models of CIPN.²⁶ Cannabinoid receptors, in particular CB₁ receptors, can alter the activity of GABAergic and glutamatergic signaling in the brain and spinal cord.⁵⁰ In rats, a mixed CB₁ and CB₂ receptor agonist suppressed nociception via a CB₁ specific mechanism⁵¹ as well as vincristine associated neuropathy via CB₁ and CB₂ receptor activation.⁵² In another rat model, a CB₂ selective agonist attenuated painful neuropathy induced by paclitaxel.⁵³ The authors suggest that activation of CB₂ suppresses nociception and central sensitization in a variety of tissue and nerve injury models of persistent pain.⁵⁴ Neuropathic pain may also involve abnormal hyper-excitability in skin afferent nerves. Skin cells express CB₂ and endothelin receptors, and when activated, release B-endorphin, which can reduce hyperalgesia mediated by pro-inflammatory pathways.^{55,56}

An additional potential mechanism of CB₁ and CB₂ receptor activation leading to suppression of neuropathic pain is from modulation of immune system function. THC and the endocannabinoid system can inhibit the release of pro-inflammatory cytokines throughout the inflammatory response, by targeting T and B cells, and macrophage activity.²⁹

Similar to CB₁ and CB₂ receptors agonists, the neuroprotective and anti-inflammatory properties of CBD provide a potential mechanism for the protective effects of CBD in neuropathic pain, including CIPN.⁵⁷ For example, CBD has been shown to directly or indirectly modulate several

receptors involved in modulating pain signaling, including 5-HT_{1A},³⁴ and transient receptors TRPV1 and TRPA1.^{28,31} TRPV1 receptors are present in sensory peripheral nerves as well as keratinocytes and are activated by capsaicin, as well as by endogenous cannabinoids.⁵⁸ Capsaicin is a TRPV agonist that has been extensively studied in pain and has activity in treating neuropathic pain. It leads to overstimulation and desensitization of nociceptors and may lead to nerve regeneration and restoration.⁵⁹ A placebo-controlled, double-blinded, crossover trial of a capsaicin cream demonstrated that it substantially decreased chronic post-surgical scar pain and its benefit persisted after stopping the capsaicin.⁶⁰ CBD may also act as a neuroprotective agent as a result of direct antioxidant activity.⁶¹ During secondary injury, CBD can reduce intracellular calcium levels and have neuroprotective effects.⁶² CBD reduces mitochondrial damage during events of cellular stress, thereby diminishing generation of inflammatory and oxidative products.⁶³ CBD also inhibits microglial proliferation and pro-inflammatory cytokines and increases anti-inflammatory cytokine production in vivo.^{31,32,64}

Patients in this case report reporting benefit were using both topical CBD alone (n=12) and a combination of CBD/THC topicals (n=10). Given that CBD is a negative modulator of CB1, it would seem that topical THC working via a CB1 mechanism would not be involved in anti-nociception. The role of CBD and THC or the combination would need to be studied in a clinical trial to determine the contribution of each compound toward pain relief. Cannabis contains not only CBD and THC but many other cannabinoids and terpenoids which appear to play a role in its activity. The “entourage effect” describes the synergy of all of the compounds observed when using whole plant-based products which may be more effective than isolated compounds.⁶⁵ However, conducting research using THC and/or whole plant extracts is very difficult given federal regulations and extreme heterogeneity in types and concentrations of products.

This case series has limitations given the retrospective nature of the study, the lack of control groups, and wide heterogeneity of products used by patients. The placebo effect has also been demonstrated in a study in which an experimental product was shown to help symptoms regardless of whether subjects received cannabis or not.⁶⁶ However, experience in the clinic suggests that more patients surveyed responded to topical cannabis products than did not and provides the rationale for proceeding with a randomized placebo-controlled trial using a standardized product to determine the actual efficacy of such treatment.

Conclusions

This case series suggests that cannabinoids may be helpful for patients with chemotherapy-induced peripheral neuropathy. This paper also discusses the potential mechanisms of

action by which topical cannabinoids might alleviate established CIPN symptoms. Noting that there is wide heterogeneity in the concentration and type of cannabis in topical creams available, a randomized placebo-controlled trial of a standardized product is needed to determine the actual utility of this approach for treating CIPN. Work is ongoing to develop such.

Authors Note

Stacy D'Andre now affiliated to Mayo Clinic, Rochester, MN, USA.

Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate/Publish

This case series was approved by the Sutter Health Expedited Review Committee, San Francisco, CA, May 14, 2020. Written consent for publication was obtained by the author from the patients with detailed case reports and is located in the patient medical record.

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Availability of Supporting Data

All data collected are included in this published article.

References

1. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. *Front Mol Neurosci.* 2017;10:174. doi:10.3389/fnmol.2017.00174
2. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain.* 2014;155:2461-2470. doi:10.1016/j.pain.2014.09.020
3. Lee G, Grovev B, Furnish T, Wallace M. Medical cannabis for neuropathic pain. *Curr Pain Headache Rep.* 2018;22:8. doi:10.1007/s11916-018-0658-8
4. Gewandter JS, Dworkin RH, Finnerup NB, Mohile NA. Painful chemotherapy-induced peripheral neuropathy: lack of treatment efficacy or the wrong clinical trial methodology? *Pain.* 2017;158:30-33. doi:10.1097/j.pain.0000000000000653
5. Flatters SJL, Dougherty PM, Colvin LA. Clinical and pre-clinical perspectives on chemotherapy-induced peripheral neuropathy (CIPN): a narrative review. *Br J Anaesth.* 2017; 119:737-749. doi:10.1093/bja/aex229

6. Blanton HL, Brelsfoard J, DeTurk N, et al. Cannabinoids: current and future options to treat chronic and chemotherapy-induced neuropathic pain. *Drugs*. 2019;79:969-995. doi:10.1007/s40265-019-01132-x
7. Zajączkowska R, Kocot-Kepska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci*. 2019;20:1451. doi:10.3390/ijms20061451
8. Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL. Mechanism of cancer pain. *Mol Interv*. 2010;10:164-178. doi:10.1124/mi.10.3.7
9. Sherif MA, Cortes-Briones JA, Ranganathan M, Skosnik PD. Cannabinoid-glutamate interactions and neural oscillations: implications for psychosis. *Eur J Neurosci*. 2018;48:2890-2902. doi:10.1111/ejn.13800
10. Omran M, Belcher EK, Mohile NA, et al. Review of the role of the brain in chemotherapy-induced peripheral neuropathy. *Front Mol Biosci*. 2021;8:693133. doi:10.3389/fmolb.2021.693133
11. 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;46:207-218. doi:10.1016/j.jpainsymman.2012.07.014
12. Brown D, Watson M, Schloss J. Pharmacological evidence of medicinal cannabis in oncology: a systematic review. *Support Care Cancer*. 2019;27:3195-3207. doi:10.1007/s00520-019-04774-5
13. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general Harms. *Ann Intern Med*. 2017;167:319-331. doi:10.7326/m17-0155
14. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9:506-521. doi:10.1016/j.jpain.2007.12.010
15. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68:515-521. doi:10.1212/01.wnl.0000253187.66183.9c
16. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34:672-680. doi:10.1038/npp.2008.120
17. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182:E694-E701. doi:10.1503/cmaj.091414
18. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*. 2013;14:136-148. doi:10.1016/j.jpain.2012.10.009
19. Hoggart B, Ratcliffe S, Ehler E, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol*. 2015;262:27-40. doi:10.1007/s00415-014-7502-9
20. Andrae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain*. 2015;16:1221-1232. doi:10.1016/j.jpain.2015.07.009
21. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manag*. 2014;47:166-173. doi:10.1016/j.jpainsymman.2013.02.018
22. Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006;147:S163-S171. doi:10.1038/sj.bjp.0706406
23. Showalter VM, Compton DR, Martin BR, Abood ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. *J Pharmacol Exp Ther*. 1996;278:989-999.
24. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*. 2007;150:613-623. doi:10.1038/sj.bjp.0707133
25. Niesink RJ, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? *Front Psychiatry*. 2013;4:130. doi:10.3389/fpsy.2013.00130
26. Masocha W. Targeting the endocannabinoid system for prevention or treatment of chemotherapy-induced neuropathic pain: studies in animal models. *Pain Res Manag*. 2018;2018:5234943. doi:10.1155/2018/5234943
27. Vučković S, Srebro D, Vujović KS, Vučetić Č, Prostran M. Cannabinoids and pain: new insights from old molecules. *Front Pharmacol*. 2018;9:1259. doi:10.3389/fphar.2018.01259
28. Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP channels. *Front Mol Neurosci*. 2018;11:487. doi:10.3389/fnmol.2018.00487
29. Donvito G, Nass SR, Wilkerson JL, et al. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. *Neuropsychopharmacology*. 2018;43:52-79. doi:10.1038/npp.2017.204
30. Fernández-Ruiz J, Sagredo O, Pazos MR, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol*. 2013;75:323-333. doi:10.1111/j.1365-2125.2012.04341.x
31. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556:75-83. doi:10.1016/j.ejphar.2006.11.006
32. Toth CC, Jedrzejewski NM, Ellis CL, Frey WH II. Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. *Mol Pain*. 2010;6:16. doi:10.1186/1744-8069-6-16
33. Xiong W, Cui T, Cheng K, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting $\alpha 3$ glycine receptors. *J Exp Med*. 2012;209:1121-1134. doi:10.1084/jem.20120242
34. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy

- efficacy. *Br J Pharmacol.* 2014;171:636-645. doi:10.1111/bph.12439
35. Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radic Biol Med.* 2011;51:1054-1061. doi:10.1016/j.freeradbiomed.2011.01.007
 36. Kleckner AS, Kleckner IR, Kamen CS, et al. Opportunities for cannabis in supportive care in cancer. *Ther Adv Med Oncol.* 2019;11:1758835919866362. doi:10.1177/1758835919866362
 37. Behl D, D'Andre SD, Parise C. Patterns of use of medical cannabis in a community oncology clinic. *J Clin Oncol.* 2020;38:e24111-e24111. doi:10.1200/JCO.2020.38.15_suppl.e24111
 38. Pergam SA, Woodfield MC, Lee CM, et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer.* 2017;123:4488-4497. doi:10.1002/cncr.30879
 39. Martell K, Fairchild A, LeGerrier B, et al. Rates of cannabis use in patients with cancer. *Curr Oncol.* 2018;25:219-225. doi:10.3747/co.25.3983
 40. Donovan KA, Oberoi-Jassal R, Chang YD, et al. Cannabis use in young adult cancer patients. *J Adolesc Young Adult Oncol.* 2020;9:30-35. doi:10.1089/jayao.2019.0039
 41. Paudel KS, Hammell DC, Agu RU, Valiveti S, Stinchcomb AL. Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers. *Drug Dev Ind Pharm.* 2010;36:1088-1097. doi:10.3109/03639041003657295
 42. Stinchcomb AL, Valiveti S, Hammell DC, Ramsey DR. Human skin permeation of Delta8-tetrahydrocannabinol, cannabidiol and cannabiol. *J Pharm Pharmacol.* 2004;56:291-297. doi:10.1211/0022357022791
 43. Xu DH, Cullen BD, Tang M, Fang Y. The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. *Curr Pharm Biotechnol.* 2020;21:390-402. doi:10.2174/1389201020666191202111534
 44. Palmieri S, Mascini M, Ricci A, et al. Identification of Cannabis sativa L. (hemp) retailers by means of multivariate analysis of cannabinoids. *Molecules.* 2019;24:3602. doi:10.3390/molecules24193602
 45. Herman A, Herman AP. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. *J Pharm Pharmacol.* 2015;67:473-485. doi:10.1111/jphp.12334
 46. Mansour RSH, Sallam AA, Hamdan II, Khalil EA, Yousef I. Elucidation of penetration enhancement mechanism of Emu oil using FTIR microspectroscopy at EMIRA laboratory of SESAME synchrotron. *Spectrochim Acta.* 2017;185:1-10. doi:10.1016/j.saa.2017.05.026
 47. Guindon J, Lai Y, Takacs SM, Bradshaw HB, Hohmann AG. Alterations in endocannabinoid tone following chemotherapy-induced peripheral neuropathy: effects of endocannabinoid deactivation inhibitors targeting fatty-acid amide hydrolase and monoacylglycerol lipase in comparison to reference analgesics following cisplatin treatment. *Pharmacol Res.* 2013;67:94-109. doi:10.1016/j.phrs.2012.10.013
 48. Uhelski ML, Khasabova IA, Simone DA. Inhibition of anandamide hydrolysis attenuates nociceptor sensitization in a murine model of chemotherapy-induced peripheral neuropathy. *J Neurophysiol.* 2015;113:1501-1510. doi:10.1152/jn.00692.2014
 49. Khasabova IA, Khasabov S, Paz J, Harding-Rose C, Simone DA, Seybold VS. Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. *J Neurosci.* 2012;32:7091-7101. doi:10.1523/JNEUROSCI.0403-12.2012
 50. Spigelman I. Therapeutic targeting of peripheral cannabinoid receptors in inflammatory and neuropathic pain states. In: Kruger L, Light AR, eds. *Translational Pain Research: From Mouse to Man.* Chapter 5. CRC Press; 2010.
 51. Pascual D, Goicoechea C, Suardiaz M, Martín MI. A cannabinoid agonist, WIN 55,212-2, reduces neuropathic nociception induced by paclitaxel in rats. *Pain.* 2005;118:23-34. doi:10.1016/j.pain.2005.07.008
 52. Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB1 and CB2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. *Br J Pharmacol.* 2007;152:765-777. doi:10.1038/sj.bjpp.0707333
 53. Rahn EJ, Zvonok AM, Thakur GA, Khanolkar AD, Makriyannis A, Hohmann AG. Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. *J Pharmacol Exp Ther.* 2008;327:584-591. doi:10.1124/jpet.108.141994
 54. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics.* 2009;6:713-737. doi:10.1016/j.nurt.2009.08.002
 55. Peppin JF, Albrecht PJ, Argoff C, et al. Skin matters: a review of topical treatments for chronic pain. Part one: skin physiology and delivery systems. *Pain Ther.* 2015;4:17-32. doi:10.1007/s40122-015-0031-0
 56. Yesilyurt O, Dogrul A, Gul H, et al. Topical cannabinoid enhances topical morphine antinociception. *Pain.* 2003;105:303-308. doi:10.1016/s0304-3959(03)00245-8
 57. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr.* 2008;30:271-280. doi:10.1590/s1516-44462008000300015
 58. Caterina MJ. TRP channel cannabinoid receptors in skin sensation, homeostasis, and inflammation. *ACS Chem Neurosci.* 2014;5:1107-1116. doi:10.1021/cn5000919
 59. Anand P, Elsafta E, Privitera R, et al. Rational treatment of chemotherapy-induced peripheral neuropathy with capsaicin 8% patch: from pain relief towards disease modification. *J Pain Res.* 2019;12:2039-2052. doi:10.2147/JPR.S213912
 60. Ellison N, Loprinzi CL, Kugler J, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol.* 1997;15:2974-2980. doi:10.1200/jco.1997.15.8.2974
 61. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA.* 1998;95:8268-8273. doi:10.1073/pnas.95.14.8268

62. Ryan D, Drysdale AJ, Lafourcade C, Pertwee RG, Platt B. Cannabidiol targets mitochondria to regulate intracellular Ca^{2+} levels. *J Neurosci*. 2009;29:2053-2063. doi:10.1523/JNEUROSCI.4212-08.2009
63. Rajesh M, Mukhopadhyay P, Bátkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:2115-2125. doi:10.1016/j.jacc.2010.07.033
64. Kozela E, Lev N, Kaushansky N, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol*. 2011;163:1507-1519. doi:10.1111/j.1476-5381.2011.01379.x
65. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163:1344-1364. doi:10.1111/j.1476-5381.2011.01238.x
66. De Vita MJ, Maisto SA, Gilmour CE, McGuire L, Tarvin E, Moskal D. The effects of cannabidiol and analgesic expectancies on experimental pain reactivity in healthy adults: a balanced placebo design trial. *Exp Clin Psychopharmacol*. 2021. Advance online publication. doi:10.1037/pha0000465