Cannabis and cannabinoids in cancer pain management

Howard Meng[a], *Tianyang Dai*[b], *John G. Hanlon*[a,c], *James Downar*[d,e], *Shabbir M.H. Alibhai*[f], *and Hance Clarke*[a,g,h]

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.

Keywords
cancer, cannabinoid, cannabis, pain

INTRODUCTION

Cannabis has had a resurgence in its popularity in much of the western world, which has led to many jurisdictions decriminalizing cannabis for both medical and recreational purposes. The medical literature on cannabis-based medicine is constantly evolving. Despite encouraging signals from preclinical studies, the use of cannabis-based medicine within the cancer therapy clinical paradigm has been underwhelming. Although robust clinical data are lacking, cannabinoid use has been approved in several countries for certain medical indications refractory to standard therapy, including nabilone for chemotherapy-induced nausea and vomiting.

An area of further exploration has been the use of cannabis itself for treating cancer-related symptoms, including pain, chemotherapy-induced nausea vomiting, anorexia, insomnia, depression and anxiety. The use of cannabis to address these symptoms could potentially reduce pill burden on patients and transform cancer care. This review aims to provide an update on cannabis-based medicine for management of cancer-related pain.

WHAT IS CANNABIS?

Cannabis is a plant-based product made from various species within the cannabis genus. According to

[a]Department of Anesthesiology and Pain Medicine, University of Toronto, [b]Department of Family and Community Medicine, [c]Department of Anesthesia, St, Michael's Hospital, Toronto, Ontario, [d]Division of Palliative Care, University of Ottawa, [e]Department of Palliative Care, Bruyere Continuing Care, Ottawa, Canada, [f]Department of Medicine, University Health Network, [g]Department of Anesthesia, Anesthesia Pain Research Unit, Toronto General Hospital and [h]Transitional Pain Service, Toronto General Hospital, Toronto, Ontario, Canada

Correspondence to Hance Clarke, MD, PhD, Department of Anesthesia, Anesthesia Pain Research Unit, Toronto General Hospital, 200 Elizabeth Street, Eaton North 3 EB 317, Toronto, ON M5G 2C4, Canada.
Tel: +416 340 4800 ext 5679; fax: +1 416 340 3698;
e-mail: hance.clarke@uhn.ca

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KEY POINTS

- Randomized controlled trials have been conducted to investigate the efficacy of cannabis and cannabinoids in chronic pain, but only a few focused specifically on cancer pain.
- Observational study of cancer pain patients using cannabis over 6 months demonstrated decreased number of patients with severe pain and decreased number of patients using opioids.
- Cannabis as an analgesic agent may achieve a synergistic effect when coadministered with opioids and has been anecdotally used to achieve opioid-sparing effect.
- Canada represents a unique environment in which the industry has driven the population to embrace a medicine long before the science has caught up.

the World Drug Report 2019 by the United Nations Office on Drug and Crime, 188 million people used cannabis globally in 2017 [1]. As more countries decriminalize or legalize cannabis, the number of people consuming cannabis-based products will likely continue to rise. Targeted to different commercial purposes, cannabis plants have been hybridized into hundreds of strains. Different classification systems have been proposed depending on their botanical morphologies, chemotaxonomies, subjective effects and other factors. Among all the Cannabis constituents, 9-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD) are among the most abundant and well-studied cannabinoids. In addition to THC and CBD, cannabis contains more than 500 organic compounds, of which more than 100 belong to the cannabinoid family [2]. Along with terpenes and flavonoids, the collective interaction and effect of cannabinoids exert their effects on the endocannabinoid system [3].

Cannabinoid drugs currently exist in synthetic THC form as nabilone and in a near 1 : 1 ratio of plant-based THC:CBD extract as nabixomols. More recently, Epidiolex, a CBD liquid, was approved for the treatment of pediatric epilepsy conditions: Lennox–Gastault and Dravet syndromes in the United States and recently in the UK [4]. Numerous non-pharmaceutically approved cannabis products are also accessible in the countries where cannabis laws are more liberal and have created a structure for legal sale. The products range from dried plant materials, extracted oil resins from the plant that can be processed into edibles and other topical formulations. These often contain multiple cannabinoids, and can be delivered in different formulations, such as patches, gels, sprays, oils, tablets and so on.

PRECLINICAL BASIC SCIENCE

The endocannabinoid system synthesizes anandamide (AEA) and 2-arachidonoylglycerol on-demand from membrane phospholipids in the postsynaptic neuron and acts primarily in retrograde fashion on the presynaptic neuron. Endocannabinoids and phytocannabinoids act on CB1 and CB2 receptors on the presynaptic neuron producing a net inhibitory effect on cell excitability via a G protein-coupled mechanism [5].

CB1 receptors are expressed throughout the brain and spinal cord in key areas responsible for pain transmission and modulation. CB1 receptors are expressed on neurons throughout the spinothalamic pain pathway, including the dorsal root ganglia, the substantia gelatinosa of the spinal cord dorsal horn, ventral posterolateral nucleus of the thalamus, rostral-ventral medulla and cortex. It is also present in other pain modulatory areas, such as the amygdala and periaquaductal gray matter [5]. The CB1 receptors in pain pathways offer a target for pharmacological intervention. CB2 receptors are expressed on immune tissues and cells such as thymus, tonsils, lymphocytes and macrophages. THC has demonstrated analgesic effects as an agonist at CB1 and CB2 receptors. CBD has been shown to have weak agonist activity at CB2 receptor and reduces the psychotropic effects of THC [6]. Ligands of the endocannabinoid system for CB1 and CB2 can also activate TRPV-1 receptors, which detects thermal and nociceptive stimuli [7]. Given the colocalization of cannabinoid receptors, TRPV-1 receptors and along with opioid receptors, there may be considerable 'cross-talk' induced by activation of the cannabinoid system [8].

EARLY CLINICAL EVIDENCE FOR CANCER SYMPTOM TREATMENT

Randomized controlled trials have been conducted to investigate the efficacy of cannabis and cannabinoids specifically in cancer pain.

As early as 1975, Noyes *et al.* [9] published on the analgesic effect of THC oil in cancer patients. A 10-patient placebo-controlled, cross-over, dose-finding study found that 15 and 20 mg of THC provided more pain relief than placebo ($P < 0.025$). A subsequent study with 36 patients demonstrated that 10 mg THC produced a comparable amount of pain relief to 60 mg codeine, and comparable sedation to 120 mg codeine [10].

Johnson *et al.* [11] in 2010 conducted the first study on the analgesic effect of mixed cannabis extract (THC:CBD ratio 1 : 1) in opioid refractory advanced cancer pain patients. This 2-week double blinded, randomized, placebo-controlled, parallel-group study with 177 patients had three arms and showed that the patients receiving THC:CBD had a statistically significant improvement from baseline numerical rating scale (NRS) pain compared to placebo (−1.37 vs. −0.69, $P = 0.014$), whereas the THC-alone group responded similar to placebo. Twice as many patients taking THC:CBD experienced a 30% pain reduction compared to placebo ($P = 0.006$), whereas THC extract alone had similar efficacy to placebo. Patients in the THC:CBD group used on average 8.75 sprays in a self-titrated protocol resulting in the delivery of 23.6 mg THC and 21.9 mg CBD per day delivered. Approximately 60% of patients experienced mild or moderate treatment-related adverse events, including most commonly somnolence, dizziness and nausea. No serious adverse event except for one episode of syncope was related to the studied substance. Among the 177 patients, a subset of 43 patients (39 in THC:CBD group and 4 in THC group) participated in an extension study for the long-term evaluation of the mixed cannabis extract [12]. On average, patients in the THC:CBD group received 5.4 sprays per day and the analgesic efficacy and safety profile remained stable over a median use of 5.2 years.

Portenoy *et al.* [13] studied 263 patients with poorly managed cancer pain on opioids in a randomized, placebo-controlled trial of nabiximols for a period of 5 weeks. Overall, no significant difference in 30% responder rate was observed between nabiximols and placebo ($P = 0.59$). Secondary outcome analysis of average daily pain reduction demonstrated greater analgesia in patients who used nabiximols compared to placebo ($P = 0.035$). Specifically, only patients using low (1–4 sprays/day) ($P = 0.006$) and medium dose (6–10 sprays/day) ($P = 0.011$) reported greater analgesic effect for nabiximols compared to placebo.

Fallon *et al.* [14] carried out a double-blind, randomized, placebo-controlled study of nabiximols for advanced cancer pain patients with severe chronic pain despite opioid therapy in 399 patients. The design was a 2-week self-titration and tolerability phase followed by 3 weeks of treatment phase. Primary efficacy endpoint was not met and a post hoc analysis demonstrated that nabiximols were effective only in US patients ($P = 0.040$) and not in patients from other countries. US patients had lower opioid dose at baseline leading to the hypothesis of a reduced downregulation of opioid receptors resulting in synergy between cannabinoid and opioid receptors in analgesia. Improvements in quality of life questionnaires were observed for the nabiximols group, despite similar NRS between groups.

A second study had an enriched enrolment with randomized withdrawal designed to detect clinically significant analgesic effect in responders. Cancer patients self-titrated nabiximols over 2 weeks and those who had more than 15% NRS improvement over baseline were placed in 5-week treatment period. Of the 404 participants enrolled, 206 met criteria as responders and were randomized to 5-week treatment. Mean change in average daily pain NRS scores was not different between groups ($P = 0.917$) [14].

Several studies evaluated the effect of cannabis products on specific types of cancer pain. Lynch *et al.* [15] focused their pilot study of 18 patients on chemotherapy-induced neuropathic pain and demonstrated that nabiximols was beneficial with an NNT of 5. Other use of cannabinoids for cancer pain includes a case-report that highlighted the use of a topical marijuana compound for wound pain that was refractory to oral opioids and neuropathic pain management [16]. Sublingual cannabis oil (15% THC and 3% CBD) has also been successfully used in a case of chemotherapy-related muscle cramps related to the use of vismodegib for in the treatment of basal cell carcinoma [17].

CLINICAL FINDINGS

A 2018 published study recruited 380 advanced cancer pain patients with chronic pain on opioid therapy and studied the effect of nabiximols in this cohort. Patients underwent 2 weeks of self-titration followed by 3 weeks of treatment phase. The per-protocol analysis demonstrated a median of 15.5 vs. 6.3% ($P = 0.0378$) improvement in average pain score from baseline [18▪]. Posthoc subgroup analysis confirmed that nabiximols only showed treatment efficacy in patients within the United States, but not the rest of the world. The proposed hypotheses for the improved response in the US cohort was that baseline opioid use was more than 25% lower in the US subgroup and the types of cancer pain were different in the US subgroup.

A large-scale Israeli observational study of 3619 cancer patients evaluated the efficacy of cannabis products [19▪]. Seventy-seven percentage of patients reported pain with a median intensity of 8/10 at baseline. Patients were offered a mix of 16 different THC and CBD strains, which were administered through oil or inflorescence (flowers, capsules and cigarettes). After 6 months, 1997 (55%) (902 died, 682 stopped treatment and 38 switched suppliers) participants continued on cannabis treatment with

only 4.6% of patients still experiencing severe pain (>7/10) compared to 52.6% at baseline. The most common reported reasons for treatment discontinuation between 1 and 6 month marks were: no longer needed cannabis treatment (28.9%), no therapeutic effect (22.5%) and adverse effects (19.3%). The percentage of patients with 'good' quality of life increased from 18.7 to 68.5%. Opioid cessation was achieved by 36% of patients, opioid decrease was reported by 10% of patients and opioid increase was reported by 1% of patients. Overall, side-effects were experienced by 30% of patients, with dizziness, dry mouth, increased appetite, sleepiness and psychoactive effects being the most common complaints.

In a dose finding study of THC and CBD, Casarett *et al.* [20▪] tracked cancer symptoms before and after each single dose of vaporizer administered dried cannabis with a mobile app. Through the analysis of 26,150 submissions, they observed that the proportion of patients experiencing a greater than 3-point pain reduction (out of 10-point system) increases linearly with the THC proportion. Twenty percentage of patients experienced more than 3/10 pain reduction after using 0% THC, whereas 50% of patients had more than a 3/10 pain reduction after using 100% THC.

NEUROPATHIC PAIN

The neuropathic component of cancer pain may account for up to 40% of cancer pain cases [21]. Neuropathic cancer pain can occur as a result of tumor burden because of tumor invasion of nerve plexus and nerve tissue. It can also be because of treatment-related events, such as chemotherapy-induced peripheral neuropathy (CIPN), plexopathies postradiation or chronic postsurgical pain from tumor resection. CIPN acutely occurs in approximately 68% of patients in the first month of treatment and similar rates occur for chronic CIPN [22]. Unfortunately, relatively few treatments exist and are limited in efficacy [23].

Cancer patients with neuropathic pain have been shown to report higher levels of pain, greater pain interference with daily activities and have lower quality of life scores than those who did not have neuropathic pain. Unfortunately, the majority of patients with neuropathic cancer pain do not receive adjuvant neuropathic treatment [24]. Cannabinoid use in chronic neuropathic pain has been studied in several systematic reviews and meta analyses, with most concluding that cannabinoid confers analgesic effect in neuropathic pain; however, the magnitude of effect is limited and may be outweighed by the risk of adverse effects [25▪▪,26].

Several recent preclinical studies have emerged to demonstrate the efficacy of the endocannabinoid system in reducing pain in mice and rat models of paclitaxel and cisplatin-induced peripheral neuropathy [27–29]. Synthetic cannabinoid receptor agonists at CB1 and CB2 have independently been implicated in the attenuation of mechanical allodynia [27]. THC and CBD have also independently demonstrated its effectiveness in attenuating mechanical allodynia in mice because of paclitaxel-induced neuropathic pain [29]. Inhibitors of MAGL, the primary hydrolase of AEA, demonstrated dose-dependent reversal of allodynia via effects of CB1 and CB2. There appears to be several potential therapeutic pathways for CINP and further elucidation is necessary.

OPIOID USE

Opioids have been the mainstay of cancer pain management with the convenience of dose escalation as needed to achieve adequate analgesia. Opioids have been used over the years as the sole agent for management of cancer pain because of their efficacy in nociceptive pain and partial effects on neuropathic pain. However, it is increasingly clear that opioids are not a medication that should be utilized in isolation given the side-effects and the tendency to create dependence. The National Cancer Care Network (NCCN) and WHO clearly recommend other classes of medications and adjuncts in the management of neuropathic pain [30,31].

Chronic opioid use is associated with significant adverse effects that often require additional medications for symptom management, thus creating additional pill burden. Furthermore, a recent observational study over a 6-year period found that doses of opioids prescribed to patients with cancer had decreased, highlighting awareness among physicians about the risk of opioid use [32]. Although no randomized trials comparing cannabis and prescription opioids for cancer-related pain have been conducted, patients are increasingly reporting the use of cannabis as a substitute for prescription opioids [33,34].

Cannabis as an analgesic agent may achieve synergistic effects when coadministered with opioids and has been anecdotally used to achieve an opioid-sparing effect [35–37]. One cross-sectional survey of patients with chronic pain using medicinal cannabis showed a 64% decreased opioid use, decreased side-effects of medications and an improved quality of life [35]. Medical cannabinoids have been elevated to third line on the Canadian Neuropathic Pain guideline since its last update in

2014. The legalization of recreational and medical cannabis has given patients greater access and acceptance of its use [38].

ATTITUDES TOWARD CANNABIS

Acceptance of medical cannabis varies considerably among medical professionals based on specialty and area of practice. Individual states in the United States have started legalizing cannabis use although it is still illegal at the federal level. Currently, 33 states and Washington D.C. have legalized medical cannabis use. However, federally, as a Schedule I drug in the United States, cannabis is classified as having no currently accepted medical use and a high potential of abuse [39].

Two national US studies in 1990s reported that only about 30% of oncologists support the scheduling of marijuana plant products as antiemetic, whereas more than 50% of the oncologists have prescribed marinol, a synthetic THC [40,41]. Similarly, in 2005, 36% of US family physicians, general internists, obstetrician–gynecologists, psychiatrists and addiction specialists agreed with medical use of cannabis [42]. Thirteen years after the passage of medical cannabis laws in Colorado, 73% of family physicians recognize that medical marijuana can help patients with debilitating diseases; however, only 30% of them think that doctors should recommend cannabis as medical therapy [43]. The newest NCCN guidelines for adult cancer pain recognized the high prevalence of medical cannabis use in cancer patients in the United States [30]. The guideline recommended providers to assess for cannabis/cannabinoid use but fell short in providing any recommendations for its use because of limited and conflicting results from studies. The European Pain Federation (EFIC) position paper identifies that cannabis-based medicines may be reasonably considered for chronic neuropathic pain; however, its use for chronic cancer pain would be considered as individual trials [31].

CANADIAN CANNABIS LANDSCAPE

Canada has permitted the medical use of cannabis since 2001, and legalized recreational use was enacted in October 2018. Cannabis can be obtained through over a 150 licensed producers, regulated by Health Canada, the federal health regulatory body or through stores (via provincial government issued permits) or dispensaries (unregulated and illegal entities). Patients can also grow their own cannabis plants and safety testing is recommended at government-approved testing facilities.

In the context of cannabis legalization, 40% of Canadians report having used cannabis in their lifetime and 15% have used within the past year, indicating the use of cannabis for medical purposes is growing [44]. Findings from clinical trials for several painful conditions have been varied, perhaps because of suboptimal cannabis products in the Canadian marketplace and failure to consider important patient characteristics. Unfortunately, the current state of knowledge precludes physicians from being able to determine the appropriateness of cannabis-based therapy and adequately advise patients on adverse effects, type of cannabis (i.e. cannabis cultivar) or dose of cannabis to use. Every patient is effectively an *n* of 1 experiment. There is hope that this will change in the near future as the Canadian Institutes of Health Research (Canada's premier publicly funded health research granting agency) have started to create funding opportunities for cannabis research in both the basic and clinical sciences.

In a survey of Canadian physicians in 2015 [45], the need for education on cannabis in medicine was reported as strong or very strong by 64% of respondents, with highest desired knowledge levels for risks and safety. Less than half of the general physicians and specialists (36%) have authorized dried cannabis for patients, whereas more physicians (59%) have prescribed cannabinoid medications. The biggest barriers from physicians to authorize cannabis were concerns for recreational use, lack of guideline and lack of evidence. A recently completed observational study in which over 600 consecutive patients presenting to orthopedic surgeons in Toronto, Canada with a primary complaint of chronic musculoskeletal pain found that 22% of the patients used cannabis with the specific intent to manage their chronic MSK pain. Interestingly, 66% of patients using cannabis for a medical purpose were not sourcing their cannabis from a 'legal source' (i.e. a regulated licensed producer) [46]. Canada represents a unique environment in which an industry and politics has driven the population to embrace cannabis as a medication long before the medical community has embraced it, and the fact remains our evidence base is still weak in this area. Over the next 5–10 years, given Canada's legal framework and the headstart the country has been given to study cannabis and its various constituents, the responsibility will rest with the scientists, clinicians and credible industry partners to undertake rigorous research. This will enable Canadians and the rest of the world to receive high-quality results to guide research and development and clinical care pathways for cancer treatment among others.

CONCLUSION

Cancer-related symptoms, including pain, can be extremely debilitating and challenging to treat. A gap exists between current preclinical and clinical data on the efficacy of cannabinoids on cancer pain management. Although clinical efficacy of cannabinoids appears limited and low-quality data to date, many of the patients studied thus far are typically optimized on opioid therapy and are often already on neuropathic medications. Further improvement in analgesia in medically refractory patients may be difficult to achieve. As life expectancy increases as a result of improvements in cancer therapy, the chronic pain and pain disability that often ensues following chemotherapy, radiation therapy and surgery will become more prevalent. Patients are commonly prescribed high doses of opioids to treat these unintended consequences of life-saving interventions. Cannabis has shown promise in the cancer patient population not only for opioid weaning strategies, but also for achieving a better quality of life and reducing harms. What cannot be overstated is the urgent need for high-quality randomized controlled trials to properly assess the effectiveness and safety of medical cannabis, compared with placebo and standard treatments, for patients living with cancer.

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Conflicts of interest

J.G.H was a paid advisor for Canadian Cannabis Clinics until April 2017.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. World: Drug Report 2019. Vienna, Austria: United Nations; 2019.
2. Aizpurua-Olaizola O, Soydaner U, Öztürk E, *et al.* Evolution of the cannabinoid and terpene content during the growth of cannabis sativa plants from different chemotypes. J Nat Prod 2016; 79:324–331.
3. Ablin J, Ste-Marie PA, Schafer M, *et al.* Medical use of cannabis products: lessons to be learned from Israel and Canada. Schmerz 2016; 30:3–13.
4. Chen JW, Borgelt LM, Blackmer AB. Cannabidiol: a new hope for patients with Dravet or Lennox-Gastaut syndromes. Ann Pharmacother 2019; 53:603–611.
5. Hill KP, Palastro MD, Johnson B, *et al.* Cannabis and pain: a clinical review. Cannabis Cannabinoid Res 2017; 2:96–104.
6. Hudson, R., J. Renard, C. Norris, et al., Cannabidiol Counteracts the Psychotropic Side-Effects of Δ-9-Tetrahydrocannabinol in the Ventral Hippocampus through Bidirectional Control of ERK1–2 Phosphorylation. 2019. 39(44): p. 8762-8777.
7. De Petrocellis L, Ligresti A, Moriello AS, *et al.* Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol 2011; 163:1479–1494.
8. Zador F, Wollemann M. Receptome: interactions between three pain-related receptors or the 'Triumvirate' of cannabinoid, opioid and TRPV1 receptors. Pharmacol Res 2015; 102:254–263.
9. Noyes R Jr, Brunk SF, Baram DA. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol 1975; 15:139–143.
10. Noyes R Jr, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975; 18:84–89.
11. Johnson JR, Burnell-Nugent M, Lossignol D, *et al.* Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and thc extract in patients with intractable cancer-related pain. J Pain Symp Manage 2010; 39:167–179.
12. Johnson JR, Lossignol D, Burnell-Nugent M, *et al.* 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 Symp Manage 2013; 46:207–218.
13. 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; 13:438–449.
14. Fallon MT, Albert Lux E, McQuade R, *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; 11:119–133.
15. 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 Symp Manage 2014; 47:166–173.
16. Maida V. Medical cannabis in the palliation of malignant wounds: a case report. J Pain Symp Manage 2017; 53:e4–e6.
17. Kutiel TS, Vornicova O, Bar-Sela G. Cannabis for vismodegib-related muscle cramps in a patient with advanced basal cell carcinoma. J Pain Symp Manage 2018; 55:e1–e2.
18. ■ Lichtman AH, Lux EA, McQuade R, *et al.* Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symp Manage 2018; 55:179–188e1.

This clinical trial describes the improvement of pain scores in a US cohort after initiation of nabiximols.

19. ■ Bar-Lev Schleider L, Mechoulam LR, Lederman V, *et al.* Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. Eur J Intern Med 2018; 49:37–43.

This observational study describes a cohort of patients who had improvements in quality of life and reduction in opioid use following the use of cannabis products.

20. ■ Casarett DJ, Beliveau JN, Arbus MS. Benefit of tetrahydrocannabinol versus cannabidiol for common palliative care symptoms. J Palliat Med 2019; 22:1180–1184.

This retrospective cohort study describes the proportion of patients experiencing pain reduction increases linearly with the THC proportion.

21. Bennett MI, Rayment C, Hjermstad M, *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain 2012; 153:359–365.
22. 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.
23. Fallon MT. Neuropathic pain in cancer. Br J Anaesth 2013; 111: 105–111.
24. Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med 2018; 33:1058–1069.
25. ■■ Stockings E, Campbell G, Hall WD, *et al.* Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain 2018; 159:1932–1954.

A systematic review and meta-analysis assessing cannabis and cannabinoids for the treatment of various types of pain in chronic noncancer pain conditions.

26. Meng H, Johnston B, Englesakis M, *et al.* Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. Anesth Analg 2017; 125:1638–1652.
27. Mulpuri Y, Marty VN, Munier JJ, *et al.* Synthetic peripherally-restricted cannabinoid suppresses chemotherapy-induced peripheral neuropathy pain symptoms by CB1 receptor activation. Neuropharmacology 2018; 139:85–97.
28. Segat GC, Manjavachi MN, Matias DO, *et al.* Antiallodynic effect of beta-caryophyllene on paclitaxel-induced peripheral neuropathy in mice. Neuropharmacology 2017; 125:207–219.
29. King KM, Myers AM, Soroka-Monzo AJ, *et al.* Single and combined effects of Delta(9) -tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. Br J Pharmacol 2017; 174:2832–2841.
30. Swarm RA, Paice JA, Anghelescu DL, *et al.* Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019; 17:977–1007.

31. Hauser W, Finn DP, Kalso E, *et al.* European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018; 22:1547–1564.
32. Haider A, Zhukovsky DS, Meng YC, *et al.* Opioid prescription trends among patients with cancer referred to outpatient palliative care over a 6-year period. J Oncol Pract 2017; 13:e972–e981.
33. Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs: a cross-sectional study. J Pain Res 2017; 10:989–998.
34. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: a survey of authorized medical cannabis patients. Int J Drug Policy 2017; 42:30–35.
35. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016; 17:739–744.
36. Haroutounian S, Ratz Y, Ginosar Y, *et al.* The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain 2016; 32:1036–1043.
37. Meng H, Hanlon JG, Katznelson R, *et al.* The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. Can J Anaesth 2016; 63:307–310.
38. Moulin D, Boulanger A, Clark AJ, *et al.* Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014; 19:328–335.
39. Drug Scheduling. 2019, United States Drug Enforcement Administration: Springfield, Virginia: Bookworld Services.
40. Doblin RE, Kleiman MA. Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. J Clin Oncol 1991; 9:1314–1319.
41. Schwartz RH, Voth EA, Sheridan MJ. Marijuana to prevent nausea and vomiting in cancer patients: a survey of clinical oncologists. South Med J 1997; 90:167–172.
42. Charuvastra A, Friedmann PD, Stein MD. Physician attitudes regarding the prescription of medical marijuana. J Addict Dis 2005; 24:87–93.
43. Kondrad E, Reid A. Colorado family physicians' attitudes toward medical marijuana. J Am Board Fam Med 2013; 26:52–60.
44. Addiction, C.C.o.S.U.a., Canadian Drug Summary: Cannabis 2018: 1–10.
45. Ziemianski D, Capler R, Tekanoff R, *et al.* Cannabis in medicine: a national educational needs assessment among Canadian physicians. BMC Med Educ 2015; 15:52.
46. Leroux T, Maldonado-Rodriguez N, Sundararajan K, *et al.* Understanding the rate and perceived efficacy of cannabis use for the management of chronic musculoskeletal pain. In OA/CORS 2020 Annual Meeting. 2019: Montreal.