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Integrating cannabis into clinical cancer care

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ABSTRACT

Cannabis species have been used as medicine for thousands of years; only since the 1940s has the plant not been widely available for medical use. However, an increasing number of jurisdictions are making it possible for patients to obtain the botanical for medicinal use.

For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression. Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy. A pharmacokinetic interaction study of vaporized cannabis in patients with chronic pain on stable doses of sustained-release opioids demonstrated no clinically significant change in plasma opiates, while suggesting the possibility of synergistic analgesia.

Aside from symptom management, an increasing body of *in vitro* and animal-model studies supports a possible direct anticancer effect of cannabinoids by way of a number of different mechanisms involving apoptosis, angiogenesis, and inhibition of metastasis. Despite an absence of clinical trials, abundant anecdotal reports that describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate, are circulating. Human studies should be conducted to address critical questions related to the foregoing effects.

Key Words Cannabis, cannabinoids, symptom management, nausea, anorexia, pain

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INTRODUCTION

Much attention has been paid to the unearthing of the 2500-year-old mummy known as the "Siberian Ice Maiden." Discovered in 1993, her subterranean burial chamber included a pouch of cannabis among other archeologic findings[1]. Magnetic resonance imaging revealed that the princess had a primary tumour in the right breast, with axial adenopathy and metastatic disease. It is hypothesized that the cannabis was used to manage her pain and perhaps other symptoms, or even possibly as a treatment for her malignant disease.

Widely used as medicine during the ensuing millennia, cannabis disappeared from the pharmaceutical armamentarium in the 1940s as its prohibition took hold. Today, we are in the midst of what appears to be something of a medicinal cannabis renaissance, with patients across the globe gaining increased access to this potent botanical medicine. In a 2014 WebMD poll, 82% of oncologists indicated their belief that patients should have access to cannabis, ranking highest among medical subspecialists in their support[2]. Regrettably, most oncologists trained during the era of cannabis prohibition and have no knowledge of how to use the plant as medicine. In these days of targeted therapies and nanotechnology, the modern oncologist might feel somewhat ill at ease recommending a herbal intervention, notwithstanding the number of potent cytotoxic chemotherapeutic agents derived from plants.

An even more vexing concern to the oncologist is the lack of data on which to base treatment recommendations. Given the nature of the drugs that they prescribe, oncologists are used to seeing strong evidence of a favourable risk–benefit ratio before recommending a therapeutic intervention. Usually, oncology drugs have proceeded through preclinical studies, followed by the traditional phase I, II, and III analyses, before we feel comfortable adding them to our toolbox. Such data about the clinical effectiveness of medicinal cannabis are all but lacking.

In the United States, cannabis is classified as a Schedule I agent with a high potential for abuse and no accepted medical use. The study of cannabis requires a special Schedule I license from the U.S. Drug Enforcement

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Administration. In addition, the only legal source of cannabis for clinical trials is the National Institute on Drug Abuse, which has a congressional mandate to study substances of abuse only as substances of abuse. Although investigators can obtain National Institute on Drug Abuse cannabis to conduct effectiveness clinical trials, funding must come from another source. Hence, carefully controlled clinical trials of cannabis as a therapeutic agent—the sorts of trials that would satisfy a data-driven oncologist—are quite rare.

In 1986, Δ^9-tetrahydrocannabinol (THC), the most psychoactive cannabinoid in the plant, was approved as a licensed drug, dronabinol (Marinol: AbbVie, North Chicago, IL, U.S.A.), for the treatment of chemotherapy-induced nausea and vomiting. Hence, oncologists probably have the longest record of using a cannabis-based medicine. In 1992, the dronabinol indication was expanded to include treatment of the anorexia associated with AIDS wasting syndrome. In 2006, nabilone (Cesamet: Meda Pharmaceuticals, Somerset, NJ, U.S.A.) another synthetic THC that had long been available in Europe and elsewhere became available in the United States as well.

The foregoing drugs are THC alone and do not include any of the other potentially therapeutic cannabinoids, terpenoids, or flavonoids that are present in the whole plant[3]. Cannabidiol (CBD), in particular, is another of the phytocannabinoids that has been generating significant interest for its potential therapeutic effects[4]. Nabiximols (Sativex: GW Pharmaceuticals, Salisbury, U.K.) is a whole-plant extract of cannabis that has been processed to have a THC:CBD ratio of 1:1. Originally approved in Europe for the treatment of central pain associated with multiple sclerosis, this sublingual preparation has also been studied in a number of cancer-related conditions[5–8]. Because most of the information derived from clinical trials on cannabinoids in cancer is derived from studies of those licensed pharmaceuticals, the present review discusses findings from studies of those agents as well as from studies of cannabis itself.

CANNABIS FOR PAIN

To date, two types of cannabinoid receptors (seven-transmembrane domain G protein–coupled receptors) have been identified in humans and other animal species[9]. The CB1 receptor, initially identified in the brain, is found in high concentrations in areas involved in the processing of noxious stimuli. The CB2 receptor is predominantly located in cells of the immune system and likely has a role in the control of inflammation and cell proliferation.

The CB receptors are not present to react with the phytocannabinoids from cannabis alone. They exist because, on demand, humans produce endogenous cannabinoids—"endocannabinoids"—that react with the receptors, effecting changes in intracellular signalling. It has been suggested that the entire function of the system of cannabinoid receptors and endocannabinoids might be to assist in modulation of the response to pain. With that in mind, it is not surprising that an increasing body of knowledge is being developed about the effects on pain of cannabinoid medicines.

A recently published systematic review[10] considered 28 studies involving a total of 2454 participants and preparations including inhaled cannabis, dronabinol, nabilone, and nabiximols, among others. Twelve of the studies investigated neuropathic pain, and three looked at patients with cancer pain. The studies generally showed improvement in pain measures, with an overall odds ratio of 1.41 (95% confidence interval: 0.99 to 2.00) for improvement in pain with the use of cannabinoids compared with placebo. An earlier systematic review of eighteen randomized controlled trials of cannabinoids in 766 participants with chronic non-cancer pain found that fifteen of the studies reported a significant analgesic effect for the cannabinoids compared with placebo, and a number of the studies also noted improvements in sleep[11]. Another review that included six of those eighteen studies in patients with cancer-related pain also favoured cannabinoids[12].

Neuropathic pain is certainly problematic in cancer patients[13]. A systematic review of six randomized, double-blind, placebo-controlled trials of cannabinoids (five specifically addressing neuropathic pain) found evidence for the use of low-dose medical cannabis in refractory neuropathic pain in conjunction with traditional analgesics[14]. Another analysis reviewed five trials of inhaled cannabis in patients with HIV-related peripheral neuropathy and again found a positive effect for cannabis compared with placebo[15]. A recent small study[16] showed a dose–response effect for vaporized cannabis in the relief of pain from diabetic peripheral neuropathy, a huge clinical problem estimated to affect 238 million people worldwide.

With all of those impressive data suggesting that cannabinoids could be effective in peripheral neuropathy, where are the studies in patients with chemotherapy-induced peripheral neuropathy? Preclinical studies in rodent models have suggested that cannabinoids might actually be able to prevent peripheral neuropathy. Activation of the CB1 and CB2 receptors suppresses the development of vincristine-induced peripheral neuropathy in rats[17]. In mice receiving daily cisplatin, administration of anandamide (an endocannabinoid) together with an inhibitor of the fatty-acid amide hydrolase that metabolizes anandamide attenuated chemotherapy-induced peripheral neuropathy[18]. Cannabidiol pretreatment stops paclitaxel-induced neuropathy in mice[19]. To date, the only human study of a cannabis-based medicine in chemotherapy-induced peripheral neuropathy is a crossover placebo-controlled trial of nabiximols[20]. Overall, reported pain scores were not different with nabiximols and with placebo. However, on a 0–10 scale, 5 responders reported a greater than 2-point decline in neuropathic pain. That observation suggests that 5 patients have to be treated with the sublingual preparation for 1 to experience clinical benefit (an acceptable number-needed-to-treat for a neuropathic condition), suggesting that further investigation of cannabis medicines in chemotherapy-induced peripheral neuropathy is warranted. Even more exciting would be a study demonstrating the potential for cannabis to actually lower the risk for neuropathy or to prevent it from developing in the first place, as the animal models suggest.

In animal models, cannabinoids and opioids have been demonstrated to have synergistic analgesic effects[21].

Analgesic effects of cannabinoids are not blocked by opioid antagonists, suggesting that the two types of agents work through different receptors and pathways. An early study found that THC was ineffective as an analgesic on its own, but that it slightly increased the effect of morphine on 2 of 3 measures[22]. A randomized controlled trial of dronabinol in patients on opioids for chronic pain found that, compared with placebo, dronabinol reduced pain ($p < 0.01$) and increased patient satisfaction ($p < 0.05$)[23]. A randomized controlled trial of nabiximols in 359 cancer patients with poorly controlled pain despite a stable opioid regimen found that the sublingual preparation (4, 10, or 16 sprays daily for 5 weeks) reduced both pain and sleep disruption[24]. A pharmacokinetic interaction study of vaporized cannabis in 21 patients with chronic—mostly non-cancer—pain taking sustained-release morphine or sustained-release oxycodone showed no significant effect on plasma levels of the opiates, but a suggestion of enhanced analgesia[25]. However, that small study was not powered for a pain endpoint, suggesting that a larger follow-on trial is warranted[26].

Clinically, I have observed that many cancer patients benefit from adding cannabis to their pain regimen. Although the effect on chemotherapy-induced peripheral neuropathy has not been glaringly obvious, other sorts of cancer-related pain appear to respond. Patients who have been put on high doses of opiates at the end of life by their well-meaning oncologist or palliative care team frequently feel totally unable to communicate with their loved ones in their precious remaining time because of altered cognition. Many have successfully weaned themselves down or off their opiate dose by adding cannabis to their regimen. Although it would seem that THC-dominant strains of cannabis would be most likely to have analgesic effects, patients often report significant pain reduction from strains that are predominantly CBD-rich. Although CBD does not actually bind to the CB1 receptor, it does block the fatty-acid binding protein that transports the endocannabinoid intracellularly to be hydrolyzed by the fatty-acid amide hydrolase, hence allowing the endogenous cannabinoid complexed with the receptors to persist[27].

CANNABIS FOR NAUSEA

As an oncologist practicing medicine in San Francisco since the early 1980s, I have often said that I need a clinical trial to demonstrate that cannabis is an effective antiemetic about as much as I need a placebo-controlled trial to demonstrate that penicillin is an antibiotic! It would appear that, if the single most active constituent of the plant is licensed and approved for treatment of chemotherapy-induced nausea, that the parent botanical should also work. Being aware that the plural of anecdote is not evidence, I would like to share an e-mail message from a 42-year-old gentleman with metastatic colon cancer requesting a renewal of his medical cannabis authorization:

> *Although I did not use it until my last 5 sessions of chemo (me getting over the stigma of its use), it did what no other drug could do, completely solve the severe nausea I had.*
>
> *It allowed me to play with my children, attend their sports and school functions, and just function very normally in day to day activities.*
>
> *I cannot thank you enough for giving me that option!*
>
> *I am currently on a chemo vacation after a clean scan, and the only time I use medical marijuana now is when I have trouble sleeping. I would like to continue to use it for that purpose instead of relying on pharmaceutical options like zolpidem etc.*

That message is representative of what many patients have recounted to me over the past 30-plus years of oncology practice in a locale in which patients have never had difficulty accessing cannabis. However, data from controlled clinical trials of cannabis are less impressive.

Only three trials have looked at cannabis in the treatment of chemotherapy-induced nausea and vomiting, and in two of them, cannabis was made available only after dronabinol had already failed. The first trial noted a significant benefit for cannabis compared with placebo in patients receiving high-dose methotrexate[28]. A later study by the same investigators made cannabis available to patients receiving cyclophosphamide or doxorubicin after dronabinol failure, and no beneficial effect was noted[29]. The third study investigating cannabis was a randomized crossover trial in 20 patients who received dronabinol and cannabis[30]. Overall, 5 of the patients reported a positive antiemetic response. Of the entire cohort, 4 patients preferred smoked cannabis, 7 preferred dronabinol, and 9 had no preference. A recent phase II investigation in 16 patients of nabiximols, the sublingually delivered whole-plant extract, found that 4.8 sprays daily was more effective than placebo in conjunction with standard antiemetics[31].

Data from studies investigating the synthetically available versions of Δ^9-THC have provided more convincing evidence. A quantitative systematic review[32] that included 30 randomized comparisons of oral nabilone, oral dronabinol, or the intramuscular levonantradol preparation (no longer available) with placebo in 1366 patients receiving chemotherapy found that, as antiemetics, cannabinoids were more effective than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride (risk ratio: 1.38; 95% confidence interval: 1.18 to 1.51). For complete control of nausea, the number needed to treat was 6, and it was 8 for complete control of vomiting. In crossover trials, the patients preferred cannabinoids for future chemotherapy cycles. A later systematic review[33] of thirty randomized controlled trials involving 1138 patients also found that cannabinoids were more effective than placebo or conventional antiemetics in reducing chemotherapy-induced nausea and vomiting, and that patients preferred the cannabinoids. Adverse effects were noted to be more intense and to occur more frequently in patients using cannabinoids. A more recent systematic review[10] of twenty-eight randomized controlled trials (twenty-three using nabilone or dronabinol) involving 1772 participants reported an overall benefit for cannabis. A Cochrane review[34] analyzed twenty-three randomized controlled trials of cannabinoids compared with placebo

or with other antiemetic drugs. Patients were more likely to report a complete absence of nausea and vomiting with cannabis than with placebo, and there was little discernable difference between the effectiveness of cannabinoids and of prochlorperazine, metoclopramide, domperidone, and chlorpromazine. Notably, however, none of the trials involved the agents now most widely used—the serotonin 5-HT_3 antagonists. The National Comprehensive Cancer Network guidelines cautiously mention cannabinoids as a breakthrough treatment for chemotherapy-induced nausea and vomiting not responsive to other antiemetics[35].

CANNABIS FOR APPETITE STIMULATION

Although cannabis is the only antiemetic that is also orexigenic, no clinical trials investigating the plant as a treatment for cancer-related anorexia–cachexia syndrome have been conducted to date. A randomized placebo-controlled clinical trial evaluating a cannabis extract and dronabinol in 243 patients with cancer-related anorexia–cachexia syndrome found that neither preparation was superior to placebo with respect to affecting appetite or quality of life[36]. A large study of 469 advanced cancer patients randomized participants to receive the progestational agent megestrol acetate or dronabinol, or both[37]. Compared with participants in the dronabinol group, those in the megestrol arm experienced a significantly greater increase in both weight and appetite, and combining dronabinol with megestrol offered no additional benefit compared with megestrol alone. One smaller study of dronabinol in cancer patients demonstrated enhanced chemosensory perception in the treatment group compared with the placebo group[38]. In the dronabinol recipients, food tasted better, and appetite and caloric intake increased. Similarly variable and largely unimpressive results for dronabinol with respect to appetite and weight in HIV-associated wasting have also been reported[39].

CANNABIS FOR CANCER

One of the lay accounts concerning the tomb of the Siberian Ice Maiden closes with these lines:

> *Modern-day scientists have increasingly been turning their attention to cannabis due to its potential to inhibit or destroy cancer cells, and at the very least, manage the pain and symptoms that come with the illness. But then, ancient people seem to have known that already.*[40]

That sort of a leap—assuming that because the Ice Maiden was buried with cannabis and had cancer, that she was using it to treat her cancer—is about as valid as the claims being made on the Internet today that highly concentrated cannabis oils can cure cancer. It might be possible, but there is, as yet, no solid evidence to support that belief. One of the more distressing situations that oncologists increasingly face is trying to counsel the patient who has a curable diagnosis, but who seeks to forego conventional cancer treatment in favour of depending on cannabis oil to eradicate their malignancy because of the large number of online testimonials from people claiming such results. Given my long practice in San Francisco, I can assume that a large proportion of my patients have used cannabis during their journey. If cannabis cured cancer, I would have a lot more survivors in my practice today. Granted, inhaled cannabis cannot deliver the concentration of active ingredients that a heavily concentrated THC or CBD oil can, but there is as yet no convincing demonstration that the *in vitro* or animal model findings translate into the clinical arena.

One of the earliest studies suggesting that cannabinoids might have anticancer activity came from the U.S. National Cancer Institute in a paper published in 1975[41]. Investigators reported that Δ^9-THC, Δ^8-THC, and CBD inhibited the growth of Lewis lung adenocarcinoma cells *in vitro* and in mice. For unclear reasons, that line of research was not pursued further at the National Institutes of Health in the United States, but was subsequently picked up by investigators in Spain and Italy, who have made enormous contributions to the field.

If cannabinoids are postulated to have a potential anticancer effect working through the CB1 receptor, it would follow that the brain—where the CB1 receptor is the most densely populated seven-transmembrane domain G protein–coupled receptor—would be a good place to start the investigation. And, in fact, numerous studies *in vitro* and in animal models have suggested that cannabinoids can inhibit gliomas[42]. Other tumour cell lines are also inhibited by cannabinoids *in vitro,* and cannabinoid administration to nude mice curbs the growth of various tumour xenografts representing multiple solid and hematologic malignancies, including adenocarcinomas of the lung, breast, colon, and pancreas, and also myeloma, lymphoma, and melanoma[43,44].

A discussion of the mechanism of action of cannabinoids as anticancer agents is beyond the scope of the present article, but has been reviewed elsewhere[45–48]. Cannabinoids appear to induce apoptosis, probably through interaction with the CB1 receptor. Cannabinoid administration in mouse models has been observed to reduce the expression of vascular endothelial growth factor and its receptors, leading to inhibition of angiogenesis. Cannabinoids also decrease the activity of matrix metalloproteinase 2, leading to decreased tumour-cell invasiveness and decreased potential for metastasis. In addition, cannabinoids have anti-inflammatory and antioxidant properties that are also desirable in combatting cancer. *In vitro* studies have demonstrated that, combined with gemcitabine, cannabinoids further reduce the viability of pancreatic cancer cells[49]. In mice, adding THC to temozolomide (used widely in treatment of aggressive brain tumours), reinstated glioma suppression in tumours that had become resistant to chemotherapy[50]. The addition of CBD enhanced the antitumour activity even when lower doses of THC were used. Similarly, a combination of THC and CBD was found to enhance the antitumour effects of radiation in a murine glioma model, suggesting that cannabinoids might be synergistic with radiation therapy as well as with chemotherapy[51].

But again, mice and rats are not people, and what is observed *in vitro* does not necessarily translate into clinical medicine. The preclinical evidence that cannabinoids

might have direct anticancer activity is provocative as well, but more research is warranted. Hence, the oncologist advising patients on the use of cannabinoids during conventional cancer treatment should be aware of the preclinical findings and should not reflexively advise patients to avoid cannabis altogether. Currently, we can be confident that cannabis could have utility in symptom management for patients living with and beyond cancer[52–54]. Compared with most of the therapeutic agents that oncologists use in their practice, the side-effect profile of cannabis as medicine is acceptable, and the adverse effects are well described[54,55]. To be able to suggest a single agent that could hold benefit in the treatment of nausea, anorexia, pain, insomnia, and anxiety instead of writing prescriptions for 5 or 6 medications that might interact with each other or with cancer-directed therapies seems advantageous. And although botanical–pharmaceutical interactions for other drugs metabolized by certain cytochrome P450 isoforms is a theoretical possibility, no significant perturbations in the plasma concentrations of prescription medications have been seen to date when cannabis is co-administered. The only published study investigating medicinal cannabis with chemotherapeutic agents found no effect on the plasma pharmacokinetics of irinotecan or docetaxel when cannabis was administered as a herbal tea, although that delivery system is neither particularly popular nor likely potent[56]. The pharmacokinetics of ingested compared with inhaled cannabis would support an inhaled route of administration if patients desire more control over the onset, depth, and duration of the effect.

CONCLUSIONS

The august *New England Journal of Medicine* published a perspective piece describing Marilyn, a 68-year-old woman with metastatic breast cancer seeking medical cannabis from her physician[57]. Interestingly, the pro and con sides of the argument were both presented by mental health practitioners and not by medical oncologists. In a follow-up blog poll, the authors reported finding it surprising that 76% of the 1446 physicians responding from around the world were in favour of medicinal cannabis, even though many came from jurisdictions in which it is totally illegal[58]. The authors of a later WebMD survey of 1566 physicians in the United States reported that 82% of oncologists and hematologists were in favour of patients having access to medical cannabis—representing the strongest approval among all medical subspecialties[2].

To summarize, cannabis and cannabinoids are useful in managing symptoms related to cancer and its treatment. Exciting preclinical evidence suggests that cannabinoids are not only effective in the treatment but also in the prevention of chemotherapy-induced peripheral neuropathy. Cannabinoids could be synergistic with opioids in the relief of pain. The safety profile of cannabis is acceptable, with side effects that are generally tolerable and short-lived. Preclinical data suggest that cannabinoids could have direct antitumour activity, possibly most impressive in central nervous system malignancies. Clinical data about the effects of cannabis concentrates on cancer are as yet unavailable. Oncologists could find cannabis and cannabinoids to be effective tools in their care of patients living with and beyond cancer.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare the following interests: I have received fees as an advisory board member for ABcann Medicinals, MMJ PhytoTech, Tikun Olam, and Zynerba Pharmaceuticals.

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REFERENCES

1. Mosbergen D. Now We Know What Killed the Ancient "Ice Princess", and Why She Had That Marijuana [Web article]. New York, NY: The Huffington Post; 2014. [Available at: http://www.huffingtonpost.com/2014/10/16/siberian-ice-princess-cancer-cannabis_n_5993052.html; cited 19 December 2015]
2. Rappold RS. Legalize Medical Marijuana, Doctors Say in Survey [Web article]. Atlanta, GA: WebMD; 2014. [Available at: http://www.webmd.com/news/breaking-news/marijuana-on-main-street/20140225/webmd-marijuana-survey-web; cited 19 December 2015]
3. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid–terpenoid entourage effects. *Br J Pharmacol* 2011;163:1344–64.
4. Massi P, Solinas M, Cinquina V, Parolaro D. Cannabidiol as potential anticancer drug. *Br J Clin Pharmacol* 2013;75:303–12.
5. Rog DJ, Nurmikko TJ, Fride T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65:812–19.
6. Duran M, Perez E, Abanades S, *et al.* Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 2010;70:656–63.
7. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. 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 Symptom Manage* 2010;39:167–78.
8. 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 Manage* 2014;47:166–73.
9. Pertwee RG, Howlett AC, Abood ME, *et al.* International Union of Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev* 2010;62:588–631.
10. Whiting PF, Wolff RF, Deshpande S, *et al.* Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313:2456–73.
11. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. *Br J Clin Pharmacol* 2011;72:735–44.
12. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med* 2009;10:1353–68.
13. Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: a review. *JAMA* 2015;314:2172–81.
14. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic

noncancer pain: systematic review or randomized controlled trials. *Can Fam Physician* 2015;61:e372–81.
15. Andreae MH, Carter GM, Shaparin N, *et al.* Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain* 2015;16:1221–32.
16. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain* 2015;16:616–27.
17. 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;152:765–77.
18. Khasabova IA, Khasabov S, Paz, Harding-Rose C, Simone DA, Seybold VS. Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. *J Neurosci* 2012;32:7091–101.
19. 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;171:636–45.
20. 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 Manage* 2014;47:166–73.
21. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci* 2004;74:1317–24.
22. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain* 2003;105:79–88.
23. Narang S, Gibson D, Wasan AD, *et al.* Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9:254–64.
24. 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;13:438–49.
25. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid–opioid interaction in chronic pain. *Clin Pharmacol Ther* 2011;90:844–51.
26. Ware MA. Clearing the smoke around medical marijuana. *Clin Pharmacol Ther* 2011;90:769–71.
27. Elmes MW, Karzocha M, Berger WT, *et al.* Fatty acid-binding proteins (FABPS) are intracellular carriers for Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *J Biol Chem* 2015;14:8711–21.
28. Chang AE, Shiling DJ, Stillman RC, *et al.* Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 1979;91:819–24.
29. Chang AE, Shiling DJ, Stillman RC, *et al.* A prospective evaluation of delta-9-tetracannabinol as an antiemetic in patients receiving Adriamycin and Cytoxan chemotherapy. *Cancer* 1981;47:1746–51.
30. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *J Ethnopharmacol* 2006;105:1–25.
31. Duran M, Perez E, Abanades S, *et al.* Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 2010;70:656–63.
32. Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001;323:16–21.
33. Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl)* 2008;17:431–43.
34. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev* 2015;11:CD009464.
35. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Antiemesis*. Ver. 2.2015. Fort Washington, PA: NCCN; 2015. [Current version available online at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf (free registration required); cited 19 December 2015]
36. Strasser F, Luftner D, Possinger K, *et al.* on behalf of the Cannabis-In-Cachexia-Study-Group. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia–cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 2006;24:3394–400.
37. Jatoi A, Windschitl HE, Loprinzi CL, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20:567–73.
38. Brisbois TD, de Kock IH, Watanabe SM, *et al.* Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* 2011;22:2086–93.
39. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Syst Rev* 2013;4:CD005175.
40. Holloway A. Did ancient Siberian princess use cannabis to cope with breast cancer? [Web article]. London, UK: Ancient Origins; 2014. [Available at: http://www.ancient-origins.net/news-history-archaeology/did-ancient-siberian-princess-use-cannabis-cope-breast-cancer-002207; cited 19 December 2015]
41. Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. *J Natl Cancer Inst* 1975;55:597–602.
42. Velasco G, Galve-Roperh I, Sanchez C, Blazquez C, Guzman M. Hypothesis: cannabinoid therapy for the treatment of gliomas? *Neuropharmacology* 2004;47:315–23.
43. Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. *Nat Rev Cancer* 2012;12:436–44.
44. McAllister SD, Soroceanu L, Desprez PY. The antitumour activity of plant-derived non-psychoactive cannabinoids. *J Neuroimmune Pharmacol* 2015;10:255–67.
45. Massi P, Solinas M, Cinquina V, Parolaro D. Cannabidiol as potential anticancer drug. *Br J Clin Pharmacol* 2013;75:303–12.
46. Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. *Oncotarget* 2014;5:5852–72.
47. Abrams DI, Guzman M. Cannabis in cancer care. *Clin Pharmacol Ther* 2015;97:575–86.
48. United States, Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI). Cannabis and Cannabinoids—for health professionals (PDQ) [Web page]. Bethesda, MD: NCI; 2015. [Available at: http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq; cited 11 December 2015]

49. Donadelli M, Dando I, Zaniboni T, *et al.* Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism. *Cell Death Dis* 2011;2:e152.
50. Torres S, Lorente M, Rodriguez-Fornes F, *et al.* A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol Cancer Ther* 2011;10:90–103.
51. Scott KA, Daigleish AG, Liu WM. The combination of cannabidiol and Δ^9-tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model. *Mol Cancer Ther* 2014;13:2955–67.
52. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. *Support Care Cancer* 2003;11:137–43.
53. Bowles DW, O'Bryant CL, Camidge R, Jimeno A. The intersection between cannabis and cancer in the United States. *Crit Rev Oncol Hematol* 2012;83:1–10.
54. Kramer JL. Medical marijuana for cancer. *CA Cancer J Clin* 2015;65:109–22.
55. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. *Pharamcotherapy* 2013;3:195–209.
56. Engels FK, de Jong FA, Sparreboom A, *et al.* Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* 2007;12:291–300.
57. Bostwick JM, Reisfield G M, DuPont RL. Medicinal use of marijuana. *N Engl J Med* 2013;368:866–8.
58. Adler JN, Colbert JA. Clinical decisions. Medicinal use of marijuana—polling results. *N Engl J Med* 2013;368:e30.