Medical cannabis: weeding out stigma and cultivating evidence

In April 2018, Vincent Maida, MD, MSc, CCFP(PC), FCFP, ABHPM, gave a keynote presentation at the Annual Meeting of the Canadian Association of Medical Oncologists. Oncology Exchange *presents a summary of his talk.*

This presentation explores the role of cannabis-based therapies in meeting the pain and symptom management needs of cancer patients. I will review knowledge of our bodies' endocannabinoid system, which is very recent and even today is often bypassed in medical school curricula. Finally, I will discuss the range of cannabis-based therapies, both pharmaceutical and botanical, describe their multiple routes of administration, and address dosing issues.

As a physician, my personal goals are to empower physicians to manage their patients' cannabinoid therapies. Some of the disturbing trends I see are patients being referred to cannabis clinics from cancer centres, or being treated by illegal dispensaries, because physicians, oncologists and palliative care specialists are not taking this domain into their own hands.

WHAT DO WE KNOW ABOUT CANNABINOIDS?

We have seen exponential growth in the number of papers on the use of cannabis in cancer care in peer-reviewed journals, from nothing in 1970 to some 140 today on Medline. A main reason is that patients continue to have significant unmet needs, despite the recent advances in cancer care. Patients are still suffering intolerable pain, opioid-related side effects, nausea and vomiting, anorexia/cachexia, not to mention anxiety and depression.

Medical cannabis is not a panacea, but offers a number of very versatile agents that have a range of activity and can be used as multipurpose adjuvants or "optimizers" of pain and polysymptom management, especially in the context of symptom clusters. Symptom clusters in cancer patients are interrelated symptoms that occur simultaneously and exert negative impacts on survival, quality of life and quality of death.[1]

A BIT OF HISTORY

Cannabis has been used for at least the last 7,000 years by many cultures that have employed it for food, fibre, and medicinal purposes. The Siberian Ice Maiden mummy, dating from the 5th century BC, is the first archaeological evidence of the use of cannabis in cancer care: the maiden who, it was found, had metastatic breast cancer, was buried with a little purse containing cannabis flowers.

Sir William Osler, 100 years ago, dabbled in cannabinoid science. Osler discovered through observational studies that a particular product, "Tincture 17" of cannabis, was effective not only in treating the pain of migraine headaches, but also in preventing migraines. Today, we know that this is due to the effects produced by tetrahydrocannabinol (THC) and cannabidiol (CBD) on the 5-hydroxytryptamine (5-HT) system, which includes serotonin receptors.

In the 20th century, we fell into the dark ages of cannabis prohibition. The movie *Reefer Madness* (1936) was a key prompt for criminalizing cannabis. Interestingly, it was created as a propaganda piece by the US government, the newspaper tycoon William Randolph Hearst, and the conglomerate DuPont. Prohibition put an end to research. However, in 1964, Raphael Mechoulam of the Hebrew University of Jerusalem, a professor of medicinal chemistry who I believe deserves to win a Nobel Prize some day, identified the chemical nature of THC and, in 1990, identified cannabinoid (CB) receptors. It was the discovery of the receptors and the endocannabinoid system that really validated the role of cannabis in therapeutics.

MEDICAL CANNABIS IN CANADA

In Canada, cannabis has been available for medical purposes since 2001, with a number of revisions to the regulations over time, most recently in 2014 with the Marijuana for Medical Purposes Regulations (MMPRs). In 2001, a patient could have access to dried marijuana directly from Health Canada's supply, or apply for a personal use/production license, or designate someone to cultivate for them with a production license. In 2014, this changed, and since then medical marijuana has been available only through commercial licensed producers, to patients who receive authorization from a physician. Health Canada committed to monitoring the content and purity of the product.

A landmark Supreme Court ruling in June 2015 involved a baker named Owen Smith who was baking with dried cannabis flowers (buds) for medical purposes instead of vaporizing it. He was arrested, and the case went all the way to the Supreme Court, which ruled that the definition of medical cannabis be expanded beyond the dried form suitable for smoking or vaporization, and include extracts and derivatives. In 2016, another landmark case, Neil Allard vs Canada, allowed patients to grow cannabis plants for personal medicinal use.[2]

Dr. Vincent Maida is Associate Professor at the University of Toronto; Consultant in Palliative Medicine & Wound Management Palliative at the William Osler Health System, Toronto; and Medical Director of Hospice Vaughan, in Vaughan, Ontario. His interest in the area of cannabis therapeutics dates back to a Palliative Medicine conference 25 years ago, organized by the Cleveland Clinic that included lectures by Dr. Mel Davis (Cleveland Clinic), Dr. Donald Abrams (University of California San Francisco) and Prof. Robert Twycross (Oxford University).

Canadians are the biggest consumers in the world of cannabis in all its forms. Statistics Canada data show how prolific cannabis consumption is in this country, however it is interesting to note that, while consumption has remained fairly constant among teenagers since 1970, among 45 to 64 years olds it has increased from next to nothing to close to 200 tons per year in 2015. Physicians need to become comfortable and confident in counselling patients about cannabinoid therapies because more and more patients, especially in cancer care, are asking about the potential of these therapies. If treating clinicians cannot deal with this issue, patients are at increased risk of obtaining faulty information.

MEDICAL AND RECREATIONAL CANNABIS

People use recreational marijuana to get high, while the aim with medical cannabis is symptom relief. A certain relaxation and euphoric effect might be desirable for some patients with advanced cancer, however that is not the main objective of using medical cannabis.

Medical cannabis is grown, processed and distributed according to Health Canada guidelines and Canadian law. Health Canada licences producers and makes sure that the supply from these 80 or so producers conforms to the stipulations in place. Medical cannabis is pure, sterile and standardized.

The 200 or so cannabis strains registered by Health Canada are the only ones that can be obtained legally for medical purposes. These show reproducible effects, meaning that patients get the exact same effect with each dose. Recreational marijuana is much more variable.

THE SCIENCE OF CANNABINOIDS

The human endocannabinoid system (ECS) is a signalling system that has survived millions of years of human evolution; along with the opioid signalling system, it is one of only 2 internal chemical systems to have survived that long. There are 10 times more cannabinoid receptors than opioid receptors in our bodies, and we have recently discovered that the endocannabinoid system is unique in that the receptors are both extracellular and intracellular.

The 2 main receptors are the cannabinoid type 1 (CB1) and type 2 (CB2) receptors. CB1 is mostly located in the central nervous system and acts as a neuromodulator, whereas the CB2 receptor is located primarily in the immune system and serves an immunomodulatory purpose. The brainstem has very few endocannabinoid systems, which is why, unlike opioids, nobody will ever die directly from an overdose of cannabis. Of particular interest in my work is the endocannabinoid system in human skin. This is an exciting area with the potential to help millions of people around the world.

The term "cannabinoid" is very general, used to describe botanical cannabinoids from plant sources, endogenous cannabinoids that bind to our receptors, and the pharmaceuticals nabilone (Cesamet), dronabinol (Marinol), and THC + CBD (Sativex). What really distinguishes medical cannabis from the pharmaceuticals is something called the "entourage effect."[3] Patients who have experienced positive effects from the pharmaceuticals Sativex (for neuropathic pain, etc), nabilone (for nausea), and dronabinol (for anorexia in human immunodeficiency virus [HIV], etc.), will have an even more robust response to medical cannabis, with fewer side effects, because it also contains terpenes, flavonoids and other cannabinoids.

Both THC and CBD are able to antagonize NMDA (N-methyl-D-aspartic acid), an amino acid derivative and specific agonist for the NMDA receptor, important for controlling synaptic plasticity and memory function. NMDA activation is one of the more significant drivers of chronic pain: patients who are on escalating doses of opioids exhibit hyperalgesia and NMDA activation, and these are the types of patients who should be top of mind for cannabinoid therapy.

CLINICAL ACTIVITY

Both THC and CBD have analgesic and antiinflammatory capacities; THC has antispasmodic, orexigenic, vasodilating and sedative actions, while CBD has antioxidant, antiepileptic and antipsychotic capacities, and is neuroprotective and sedative. CBD counteracts many of the troublesome psychotomimetic side effects produced by psychoactive THC. THC has a very narrow therapeutic window, meaning that using too little will have no effect, while too much will produce side effects. CBD negates a lot of these side effects, thereby broadening the therapeutic window. Even patients who have previously had bad experiences with THC recreationally will probably have fewer of those side effects if more CBD is added to their medical cannabis regimen.

Cannabinoid pharmacology

The effect of eating a fresh cannabis bud is minimal, because the THC and CBD contained in the raw material is in acid form. When THC and CBD are heated through smoking, vaporizing or cooking, decarboxylation occurs: the acid forms of THC and CBD lose CO_2 and become the non-acid forms, which are much more powerful in terms of effects on pain, spasticity, etc. Both THC and CBD have high lipophilicity and are distributed widely because of their high level of protein binding. Metabolism is mostly in the liver through cytochromes P450 (CYP450), and THC and CBD are excreted slowly through the digestive and urinary systems.

The route of administration influences both the onset and duration of action. Smoked or vaporized cannabis begins taking effect within 5 minutes and lasts between 2 and 4 hours. Ingested formats, prepared either as oils or teas, have a 30- to 60-minute onset of action and much longer duration, between 8 and 12 hours. The oral pharmaceutical formulations nabilone and dronabinol have an onset of action of 60 to 90 minutes and 30 to 60 minutes, respectively. Nabilone has a considerably longer duration of action (8 to 12 hours) than dronabinol (4 to 6 hours). Sativex, a mucosal oral formulation, begins taking effect within 15 to 40 minutes and lasts between 2 and 4 hours.[4]

Most of my patients combine an oral formulation as a long-acting agent and vaporized or smoked cannabis for breakthrough needs such as pain, nausea and vomiting. It is important to be creative and listen to patients to arrive at an appropriate combination of formulations.

Consultation with the hospital pharmacist is helpful to

check for potential interactions. THC and CBD can inhibit certain CYP enzymes, but over 2 decades using these agents, I have never seen a patient have a significant interaction from a CYP perspective. A more serious concern is CYP3A4, the busiest isoform of the CYP network, and drugs such as fentanyl, methadone and even, I believe, the 5-HT_3s and neurokinin 1 (NK1) agonists, which are all funneled through CYP3A4. It is important to be aware that there is some CYP enzyme inhibition, though it is quite weak. Pharmacists are valuable resources to verify potential for interaction.

Side effects

Common CNS side effects of THC include sedation, somnolence, dizziness, euphoria and blurred vision. Dry mouth is also common. Hypotension and vasodilation are common cardiovascular effects, while tachycardia and palpitations occur rarely. This is of particular concern in patients with unstable angina and other cardiovascular conditions. Medical cannabis contains much less THC, which is responsible for these side effects, than CBD.

Health Canada lists a number of contraindications and precautions for the use of medical cannabis: patients under age 25, pregnant and lactating women, and people with schizophrenia and psychosis, substance abuse issues, or certain cardiac conditions. It should not be used when driving or operating machinery, and there is also an interaction in heavy tobacco smokers that can lead to induced arteritis. And absolutely beware of using medical cannabis in patients on strong CYP3A4 inhibitors, such as ketoconazole, HIV antivirals and aprepitant (Emend).

Dosing

There are not, as yet, any dosing studies available for pharmaceutical formulations, though we know that it is highly individualized: starting low and going slow is the best way to avoid causing any harm. In patients with cancer, it is best to start medical cannabis at least 7 days prior to initiating chemotherapy, to allow patients to grow accustomed to its effects. Patients should discontinue use of tricyclic antidepressants, benzodiazepines, barbiturates, etc.

In general, there is a factor of about 2.5 between the dried smoked/vaporized bud and the orally consumed varieties (i.e. 0.75 grams inhaled = 1.875 grams ingested). Oral formulations tend to be a little more expensive because they use more material. Dosing can assume a daily dose of 1.5 grams per day for 2 vaporizer bowls, or 3.75 grams per day for oral products. The websites of licensed producers describe quite a range of available products, with strengths ranging from 20 to 200 mg of THC or CBD per gram of dried medical cannabis, and from 1 to 30 mg of THC or CBD per ml of medical cannabis oil. Prescriptions can be customized to a patient's needs. Previous use of and response to recreational cannabis is a valuable guide to potential tolerance.

MEDICAL CANNABIS IN CANCER CARE

I will focus on 3 particular areas of symptom management: pain, chemotherapy-induced nausea and vomiting (CINV), and anorexia. There is an emerging evidence base to supplement the record of safe and effective use over the entire course of recorded human history. Evidence from clinical trials has been difficult to amass under prohibition policies, however there are now 10 randomized controlled trials (RCTs) looking at pharmaceutical cannabinoids, as well as 6 RCTs of smoked cannabis. In populations with cancer, Johnson et al[5] and Porteney et al[6] found improvements in pain with a pharmaceutical combination of THC and CBD. Medical cannabis trials have found improvements in pain in populations with HIV neuropathy[7,8] and multiple sclerosis[9], as well as patients with cancer.[10]

The National Academies of Sciences, Engineering and Medicine Report, with Dr. Abrams as lead author, reviewed the highest grade of evidence and concluded that cannabinoid-based medicines (CBMs) are effective for pain, CINV and MS spasticity.[11] The Canadian Pain Society is recognizing the increasing robustness of the evidence, moving cannabinoids from fourth-line to third-line therapy for cancer-related pain in 2010,[12] and likely to move it further up the line soon.

In CINV, there have been great improvements in treatment, with the 5-HT_3 blockers spelling a real revolution in terms of managing acute CINV, and NK_1 agonists further helping in the acute phase, but also bringing benefits in the delayed phase. Therapeutic guidelines recommend behavioural treatment in the anticipatory phase, prior to receiving chemotherapy, as it does not appear to be fully addressed by the NK_1 and 5-HT_3 blockers. There is an emerging body of evidence showing that cannabinoid therapy can help patients in this anticipatory phase, as well as in acute and delayed phases. A meta-analysis by Tramer et al. achieved impressive results with nabilone in this context.[13] The National Academies meta-analysis report published a few months ago by Abrams determined there is substantial, conclusive evidence for the use of cannabis-based medicines to treat CINV.[11]

In cancer-related anorexia, unfortunately, there is not much trial evidence yet for the use of cannabinoid therapies. Although they are effective against anorexia in AIDS, megestrol is superior to cannabinoids in anorexia/cachexia syndrome in cancer. However, lack of evidence does not mean lack of efficacy. The appetite-stimulant "munchies" effect of cannabis is well known, but there are as yet no studies. In the National Academies report, Abrams lists only limited evidence for effectiveness on anorexia.

CANNABINOIDS AS CANCER TREATMENT

We are currently seeing a wave of research showing that cannabinoids hold promise for disease modulation, and patients are starting to ask if cannabis can cure cancer. The US National Institutes of Health (NIH) summarized laboratory, animal and preclinical studies of the antitumour effects of cannabinoids and identified potential mechanisms through which they may inhibit tumour growth, either by inducing cell death or by inhibiting tumour angiogenesis.[14] There is some evidence of antitumour effects in cell cultures and xenografts. As well, mouse studies suggested that CBD might enhance uptake of cytotoxic drugs into malignant cells. Only one very small study in humans has been reported, establishing safety, but coming to no conclusions regarding efficacy.[15]

A new frontier: cannabis in wound care

My own research has been looking at topical cannabinoids, applying cannabis-based medicines to painful and non-healing wounds. I have studied them in a number of patients with pyoderma gangrenosum, a very painful wound, and seen clinically significant and rapid (within 5 minutes) analgesic effects with cannabis oil, along with an opioid-sparing effect, which is especially promising given recent literature showing that opioids may inhibit wound healing. A meta-analysis conducted last year showed that, in 17 of 19 studies, morphine sulfate equivalents (MSEs) were reduced almost fourfold (3.6) when there was treatment with THC.[16]

AUTHORIZING MEDICAL CANNABIS IN CANADA

The process healthcare providers must follow to help patients obtain medical cannabis involves a consultation, to give patients a medical document stating the number of grams they require per day, which they then use to register with a licensed producer and place an order. The product is sent directly to the patient by courier. Healthcare providers do not prescribe medical cannabis — it is a botanical material and not a pharmaceutical, and therefore has no Drug Identification Number (DIN) — but rather authorize its use. The Health Canada website has detailed information along with the required forms.

The College of Physicians and Surgeons (at least in Ontario) is supportive of the use of medical cannabis, asking simply that physicians keep good documentation that the patient has continued to suffer after trying all the guideline-recommended drugs for their illness or ailment. However, the College is very strict about only using it in patients over age 25.

Regarding safety and harm reduction with medical cannabis, a systematic review by Deshpande et al[17] of the RCTs mentioned above found that its side-effect profile was very low, with some minor, well-tolerated neurocognitive effects (learning, memory, and psychomotor deficits). The only prospective study looking at medical cannabis is by Mark Ware from Montreal.[18] Although there were some minor psychomimetic and cognitive effects, these were not clinically relevant and patients were still wholly able to function. Certainly, there were no deaths: a person will never die directly from cannabis because of the lack of receptors in the brainstem.

A PAIN EPIDEMIC

Canada has the dubious distinction of having the world's highest per capita usage of medical cannabis in the 29% of the population who suffer chronic pain and the more than 50% of cancer patients who have uncontrolled pain. American states with medical cannabis programs have seen a reduction in opioid overdose mortality. A study published this year in JAMA Internal Medicine found that medical cannabis legislation is also associated with reduced opioid prescribing, as is medical cannabis legalization.[19]

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