MARIJUANA FOR MEDICAL PURPOSES

A Guide for Health Care Practitioners.

Tweed

At Tweed, We recognize that as a doctor your patients' well-being is paramount. Our goal is to support practitioners with resources as they determine the appropriate use of medical marijuana in their patients' therapies.

INSIDE:

HAVE QUESTIONS?

For more information about Tweed and marijuana for medical purposes you can visit www.tweed.com or contact the Tweed Medical Education Team at meded@tweed.com. We will gladly answer any questions you have.

Hi. Our goal is to provide you with the necessary information to understand Tweed, the support and products we can offer, and how you work with Tweed to deterimine if medical marijuana is right for your patient.

If you don't find what you are looking for in this Guide, we encourage you to reach out to us by phone or email, and Team Tweed will be happy to find the answer to your question.

THE PATIENT IS THE PRIORITY.

Patients are supported by helpful members of Team Tweed to assist them with every step along the way. Tweed pays for shipping across Canada, and was the first to offer Compassionate Pricing for those who qualify. Simply put, we believe the patient experience should be as straightforward as possible.

STRAIN VARIETY.

Patients registered with Tweed have access to a wide variety of strains. We offer this variety because cannabis is not a "one size fits all" therapy. From indica to sativa, CBD to THC, patients are able to find what is ideal for them.

PRODUCT SUPPLY.

Tweed's facility in Smiths Falls has over 168,000 square feet of growing space. We recently acquired a state-of-the-art, 350,000 square foot licensed greenhouse in Niagara-on-the-Lake. We hope you will come to trust Tweed's variety, consistency, and product availability.

SUPPORTING MEDICAL EDUCATION IN THE COMMUNITY.

At Tweed we are helping healthcare practitioners access the information they need to assess medical marijuana as a therapy. We have a team dedicated solely to medical education and outreach, and are committed to making balanced, needs-based education available.

RESEARCH.

Tweed is committed to furthering the body of knowledge around marijuana for medical purposes. We are engaged in research partnerships with the University of Ottawa and Ryerson University.

INDUSTRY LEADERSHIP.

Tweed is a founding member of the Canadian Medical Cannabis Industry Association (CMCIA). By speaking with a common voice and establishing best practices for the industry, we are working together to help bring awareness about marijuana for medical purposes to healthcare practitioners across the country.

This document provides a brief overview of the major cannabinoids present in whole marijuana. All evidence and statements in this document are sourced from the American Herbal Pharmacopoeia's Monograph on Cannabis Inflorescence.

THE MAIN COMPONENTS.

Medical marijuana consists of hundreds of chemically distinct components, all of which have unique properties. The main therapeutic components of medical marijuana are cannabinoids, which have been shown to provide patients with therapeutic benefit for indications ranging from pain management to epilepsy. The Cannabis spectrum is the balance of concentrations of the most prevalent and actively researched components of medical marijuana. The best-known and most relevant component of the cannabis spectrum is the balance of Δ^9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) concentrations within medical marijuana. This variable balance may determine the appropriateness and efficacy of certain strains of marijuana for specific indications / conditions.

It is important to note that no single component of medical marijuana alone has been isolated as the therapeutic agent and that therapeutic benefits result from the symphony of components in the plant, which is not limited to the cannabinoids.

Δ^9-TETRAHYDROCANNABINOL (THC).

THC is the main therapeutic component of marijuana. It mimics the action of a naturally occurring endocannabinoid called anandamide. THC is responsible for the psychoactive effects of marijuana. Research has linked THC to the following properties:

- Analgesic
- Antiemetic
- Appetite stimulant
- Anti-spasticity

Conversely, strains of marijuana with high proportions of THC may cause feelings of anxiety, disorientation and intoxication.

CANNABIDIOL (CBD).

As the main non-psychoactive component in marijuana, CBD is an agonist to serotonin receptors and can enhance adensosine receptor signaling by inhibiting receptor inactivity. As a result of its biological interaction, CBD has a strong role in therapies for pain and inflammation.

Research has linked CBD to the following properties:

- Anti-inflammatory
- Neuroprotective
- Anxiolytic
- Anti-seizure
- Antipsychotic

MECHANISM OF DELIVERY.

Patients DO NOT need to smoke medical marijuana to receive the therapeutic benefits it has to offer. Tweed recommends the use of a vaporizer. Vaporizing is an effective alternative to smoking which provides the same therapeutic effect while reducing exposure to harmful compounds resulting from the burning of plant matter.

EFFICACY.

Cannabis is a therapy used to treat a variety of symptoms. The therapeutic benefits of Cannabis are largely the result of the interplay between two main active components; Tetrahydrocannabinol (THC) and Cannabidiol (CBD).

DOSAGE.

The average patient consumes 1-3 grams of medical marijuana per day. The minimum dosage may be higher for certain patients and for certain indications.

STRAIN.

When beginning therapy with medical marijuana it is best to start with a strain that is lower in THC. More experienced patients may choose to try different strains varying in THC and CBD content to best address their symptoms.

If you have any questions about dosage recommendations or what strains are most beneficial for specific symptoms and conditions, please contact our medical education team and we would be happy to assist you.

EVIDENCE.

ElSohly, M., Chandra, S., Lata, H., Williamson, E., Upton, R., Harder, D., Slade, D., Radwan, M., and Li, K. (2013). Cannabis Inflorescence, Cannabis spp., identity, analysis and quality control. American Herbal Pharmacopoeia (AHP).

Gaoni and Mechoulam, 1964; Joy et al, 1999, Hampson et al, 1998; Leweke et al, 2012; Mechoulam et al, 1997; Pertwee, 2008

SATIVA.

Sativa strains are almost exclusively THC dominant. Although indica strains can also be high in THC, the therapeutic effects of THC are consistently found in sativa strains.

INDICA.

Indica strains can contain higher levels of CBD and more balanced mixtures of CBD and THC. Although not all indicas are CBD dominant, the therapeutic effects of CBD are typically found in indica strains.

HYBRIDS.

Hybrids are created by breeding two strains of cannabis together, where one strain is, in some part, Indica, and the other is, in some part, Sativa.

EVIDENCE.

ElSohly, M., Chandra, S., Lata, H., Williamson, E., Upton, R., Harder, D., Slade, D., Radwan, M., and Li, K. (2013). Cannabis Inflorescence, Cannabis spp., identity, analysis and quality control. American Herbal Pharmacopoeia (AHP).

THC & CBD.

The interplay between these two active components in marijuana is presently being heavily researched, and results to date have indicated that these compounds have an incredibly complex relationship in vivo, along with the over 700 other metabolites in whole bud marijuana. One conclusion that has been confirmed is that CBD as a non-psychoactive component of marijuana in fact tempers and reduces the psychoactive effect of the THC.

SECONDARY CANNABINOIDS.

Medical marijuana contains a number of secondary cannabinoids. There is limited evidence about the effects of these cannabinoids, although many are precursors and metabolites of the primary active components THC & CBD.

Cannabigerol (CBG)

Cannabigerolic acid (CBGA) is a precursor for both THC and CBD. CBG is commonly present in small amounts in marijuana, although some strains have been bred to increase the proportion of CBG in the plant. CBG is a non-psychoactive cannabinoid and in laboratory settings has demonstrated anti-microbial properties as well as inhibition of proliferation of keratinocytes and cancer cells.

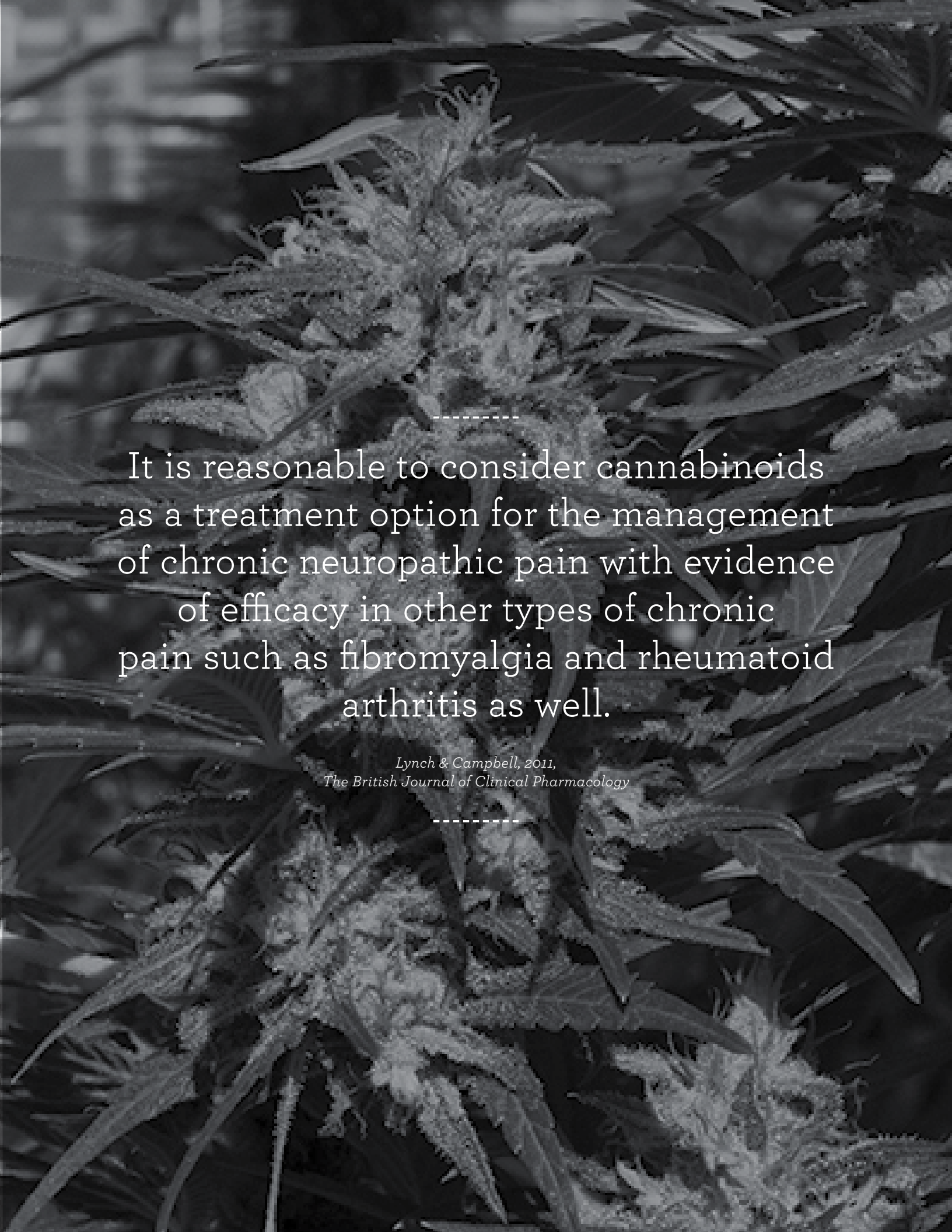
Δ8-Tetrahydrocannabinol (Δ8-THC)

Δ^8-THC, not to be confused with Δ^9-THC, is present in very small amounts in marijuana. Δ^8-THC is less psychoactive than its counterpart Δ^9-THC and at low doses is effective in stimulating appetite.

ADDITIONAL CANNABINOIDS.

A number of other cannabinoids have been isolated in the marijuana plant. To date many of the therapeutic benefits of cannabinoids have not been examined. Additional cannabinoids include:

- Cannabielsoin (CBE)
- Cannabitriol (CBT)
- Cannabichromene (CBC)
- Cannabinol (CBN)
- Cannabicyclol (CBL)
- Cannabinodiol (CBND)



It is reasonable to consider cannabinoids as a treatment option for the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well.

Lynch & Campbell, 2011,
The British Journal of Clinical Pharmacology

IN SHORT:

There are no restrictions on which patients can be supported by their doctor to access medical marijuana.

Patients are no longer required to register with Health Canada.

All medical marijuana is accessed through licensed producers.

Practitioners are now asked to designate daily quantities for patient consumption.

As before, practitioners are not obligated in any way to provide patients access to medical marijuana.

In 2001, Health Canada introduced a program to allow patients to access marijuana for medical purposes. Since the inception of this program the number of patients in the program had grown from 500 to approximately 40,000. In an effort to address the public health and safety risks of a program that was not designed to support tens of thousands of Canadians, Health Canada introduced the Marijuana for Medical Purposes Regulations (MMPR). As of April 1st, 2014 the only way for your patients to access marijuana for medical purposes is through a licensed and regulated producer. The introduction of this program now provides you as a physician the peace of mind that your patients' medicine is being produced in a licensed, clean, secure, and quality controlled environment, and that products are accurately and appropriately labelled.

WHAT'S CHANGED?

As a practitioner who may choose to grant a patient access to marijuana for medical purposes, there are a few changes to the program that you should know about. At Tweed our goal is to provide practitioners and patients with the most relevant and up to date information possible. If you have any questions about this document or any of the regulatory changes please contact our Medical Education team at meded@tweed.com.

INDICATIONS FOR USE.

The new MMPR no longer places any limitations on the conditions for which a practitioner can support access to marijuana for medical purposes.

ACCESS.

Patients are now only able to access marijuana for medical purposes through licensed producers. Medical marijuana is only accessible via secure courier (no "store front" sales are permitted). Patients have the option to have medicine shipped to their home, a practitioner's office, or a confirmed shelter/support center.

REGISTRATION.

Patients no longer need to have personal information registered and reviewed by Health Canada, as Tweed or another licensed producer of your patient's choosing now handles all registration information. This means minimal wait times and immediate access for patients.

DOCUMENTATION.
Under the new system, only two forms of documentation must be provided to a licensed producer and Health Canada is no longer required to review this process. Patients must provide:

- A Medical Document, which has been signed by their practitioner.
- A signed Registration Form.

ALLOWANCE.
As a practitioner you now have more control over the amount of marijuana your patient can access. The new Medical Document, which is submitted to licensed producers, requires that you indicate how much marijuana your patient should be using on a daily basis:

In addition to designating the daily-allowed amount of medical marijuana, practitioners are required to designate the duration of patient access, which can be up to a full calendar year.

VERIFICATION OF MEDICAL DOCUMENT.
When a patient submits a Medical Document to Tweed, we are **obligated** to contact your office to confirm the contents.

SUMMARY.
The changes as a result of the introduction of the MMPR are designed to reduce the burden of the system on patients, and to provide them with a safe and secure source for their medical marijuana. Health Canada has introduced changes that make the process easier for practitioners to provide access for patients, while simultaneously offering them more control over patient consumption.

If you have any questions about the changes to medical marijuana regulations or about Tweed, please contact our Medical Education team at meded@tweed.com.

1-3 GRAMS

Is the average patient's daily consumption of medical marijuana according to Health Canada.

STRAIN:
When beginning therapy with medical marijuana it is best to start with a strain that is lower in THC. More experienced patients may choose to try different strains varying in THC and CBD content to best address their symptoms.

If you have any questions about dosage recommendations or what strains might be most beneficial for specific symptoms and conditions, please contact our medical education team and we would be happy to assist you.

The potency and type of the marijuana chosen may impact efficacy of the therapy.

Typically strains higher in THC are considered most appropriate in the management of symptoms resulting from cancer treatment.

DID YOU KNOW?

The primary bioactive components in medical marijuana have the following boiling points:

THC: 157 °C (315 °F)
CBD: 160-180°C (320°F-356°F)
CBN: 185 °C (365 °F)

EVIDENCE.

McPartland, J. M., & Russo, E. B. (2001). Cannabis and cannabis extracts: greater than the sum of their parts?. Journal of Cannabis Therapeutics, 1(3-4), 103-132.

Hazekamp, A., Ruhaak, R., Zuurman, L., van Gerven, J., & Verpoorte, R. (2006). Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol. Journal of pharmaceutical sciences,95(6), 1308-1317.

Abrams, D. I., Vizoso, H. P., Shade, S. B., Jay, C., Kelly, M. E., & Benowitz, N. L. (2007). Vaporization as a smokeless cannabis delivery system: a pilot study. Clinical Pharmacology & Therapeutics, 82(5), 572-578.

Patients DO NOT need to smoke marijuana to receive the therapeutic benefits. Tweed recommends the use of a vaporizer. Vaporizing is an effective alternative to smoking which provides the same therapeutic effect while reducing exposure to harmful compounds resulting from the burning of plant matter.

At Tweed we believe patients should be provided with options to consume cannabis with the least potential harm. For this reason we have exclusive pricing agreements to provide registered Tweed customers with heavily discounted, high quality vaporizers.

HOW VAPORIZING WORKS.

Vaporizing requires a specialized device traditionally called a vaporizer (also known as a nebulizer), which can vary in size, make and features.

Using a vaporizer involves the placement of ground cannabis into a chamber where the cannabis is progressively heated past the boiling point of each bioactive component, but not high enough to cause the plant to burn. The vapors are collected into a secondary chamber, or are directly inhaled by the patient.

VAPOR POINTS.

Many vaporizers offer the ability to change the set temperature, which can impact the amount of bioactive cannabinoids that are present in the vapor. Research using the Volcano® vaporizer found the delivery efficiency highest at around 226°C (439 °F), falling to about half efficiency at 150°C (302 °F) to 180°C (356 °F) degrees depending on material.

Research into the management of chronic pain has yielded the largest body of evidence in support of the use of medical marijuana to date. Chronic pain can be the result of numerous conditions including mechanical back/neck pain, trauma, diabetes, cancer, multiple sclerosis, inflammatory bowel disease, arthritis, menstrual pain, and HIV/AIDS.[1] Cannabis is effective on its own, and also affords the option of combination therapy with opioids because cannabis interacts with a completely independent set of receptors in the endocannabinoid system. Additionally there is evidence to suggest that cannabis is an effective alternative in opioid dose/use reduction strategies.

EFFECTS OF MEDICAL MARIJUANA USE.

Multiple randomized control trials have evaluated the efficacy of cannabis as an analgesic, and have determined that it significantly reduces pain for patients.[1,2,3,4,5,6] Cannabis also offers the added benefit of having no known risk of overdose.[1] A 2008 University of California at Davis double blind, randomized clinical trial reported both high and low doses of inhaled cannabis reduced neuropathic pain of diverse causes in subjects unresponsive to standard pain therapies.[7] A 2010 McGill University study reported that smoked cannabis significantly improved measures of pain, sleep quality and anxiety in participants with refractory neuropathic pain for which conventional therapies had failed.[8] The efficacy of cannabis in the management of pain, coupled with no risk of overdose, has led to a strong interest from the patient community in exploring the use of medical marijuana.

EVIDENCE.

1. Noyes, R., Brunk, S. F., Avery, D. A., & Canter, A. C. (1975). The analgesic properties of delta-9-tetrahydrocannabinol. Clin Pharmacol Ther, 18(1), 84-89.

2. Lynch, M. E., & Campbell, F. (2011). Cannabinoids for treatment of chronic non cancer pain; a systematic review of randomized trials. British journal of clinical pharmacology, 72(5), 735-744.

3. Lynch, M. E., & Clark, A. J. (2003). Cannabis reduces opioid dose in the treatment of chronic non-cancer pain. Journal of Pain and Symptom Management, 25(6), 496-498.

4. Notcutt, W., Price, M., Miller, R., Newport, S., Phillips, C., Simmons, S., & Sansom, C. (2004). Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1'studies. Anaesthesia, 59(5), 440-452.

5. Ellis, R. J., Toperoff, W., Vaida, F., Van Den Brande, G., Gonzales, J., Gouaux, B., ... & Atkinson, J. H. (2008). Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial.Neuropsychopharmacology, 34(3), 672-680.

6. Ware, M. A., Doyle, C. R., Woods, R., Lynch, M. E., & Clark, A. J. (2003). Cannabis use for chronic non-cancer pain: results of a prospective survey.Pain, 102(1), 211-216.

7. Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., & Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. The Journal of Pain, 9(6), 506-521.

8. Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., ... & Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal, 182(14), E694-E701.

EVIDENCE.

1. Burns, T. L., & Ineck, J. R. (2006). Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. The Annals of pharmacotherapy, 40(2), 251-260.

2. Costa, B., Trovato, A. E., Comelli, F., Giagnoni, G., & Colleoni, M. (2007). The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. European journal of pharmacology, 556(1), 75-83.

3. Fiz, J., Durán, M., Capellà, D., Carbonell, J., & Farré, M. (2011). Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PloS one, 6(4), e18440.

4. Noyes, R., Brunk, S. F., Avery, D. A., & Canter, A. C. (1975). The analgesic properties of delta-9-tetrahydrocannabinol. Clin Pharmacol Ther, 18(1), 84-89.

5. Schley, M., Legler, A., Skopp, G., Schmelz, M., Konrad, C., & Rukwied, R. (2006). Delta 9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Current Medical Research and Opinion®, 22(7), 1269-1276.

6. Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., ... & Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal, 182(14), E694-E701.

Fibromyalgia is a chronic pain syndrome, the cause of which remains poorly understood. Fibromyalgia is characterized by widespread tenderness over multiple points in muscles and soft tissue. The pain may be caused by neuro-chemical imbalances including the activation of inflammatory pathways resulting in abnormalities in the way pain is processed.

SYMPTOMS.

Pain presents as the primary symptom for patients with fibromyalgia. The condition is also associated with symptoms of fatigue, mood and sleep disorder, and joint stiffness.

EFFECTS OF MEDICAL MARIJUANA USE.

Pain: Various studies have explored the implications of cannabis in the management of pain.[1-6] Studies have proven that there are valuable analgesic properties with cannabis use. [1,4,6] Medical marijuana is ideally suited as a component of a pain management strategy as it does not lead to harmful interactions with conventional pharmaceuticals used in pain management.[4] With respect to fibromyalgia patients, cannabis has demonstrated a statistically significant reduction in pain and stiffness, as well as enhanced relaxation and increased feelings of well being.[3,5] The anti-inflammatory properties of certain cannabinoids may be responsible for the down regulation of imbalanced inflammatory pathways associated with the pain of fibromyalgia.

Multiple Sclerosis (MS) is a neurodegenerative disease characterized by inflammation, the formation of "plaques" in the central nervous system and destruction of the myelin sheaths which cover and protect nerves throughout the body. The damage to neurons in turn prevents them from repairing and functioning properly to transmit nerve signals. The use of cannabis in the management of MS originates from the anti-inflammatory effects of cannabinoids, in conjunction with their analgesic properties. The therapeutic properties of cannabis coupled with the mild side effects in contrast to conventional medications has led many MS patients to explore the option of medical marijuana.

SYMPTOMS.

MS can have various symptoms associated with neurological damage. The extent, type, and severity of the symptoms are contingent on the location of damage to the nervous system. Symptoms include numbness and tingling (paresthesia), pain, tremors, muscle weakness, muscle spasms (spasticity), and changes to specific functions like walking (ataxia) or swallowing, and more. Medical marijuana is recognized in published literature as being effective in the management of paraesthesia, pain (acute and chronic), ataxia, spasticity and tremors.[1-9]

EFFECTS OF MEDICAL MARIJUANA USE.

Several randomized control trials (RCTs) have been published on the efficacy of cannabis and cannabinoids in the management of symptoms associated with MS.[2,4,9] Patients in these trials have demonstrated significant reductions in spasticity and pain symptoms.[2,4,9] In a 2012 randomized control trial (RCT) Corey-Bloom et al. determined that smoked cannabis reduced patient spasticity by approximately 25% in comparison to placebo.[4] The same study had patients reporting a near 50% reduction in pain.[4] More research is required to investigate the ideal potency of both Δ9-THC and CBD in symptom management of MS, however studies have indicated that patients report better symptom management with medicine containing 12.0% Δ9-THC over medicine with lower concentrations of Δ9-THC.[10]

EVIDENCE.

1. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. Mult Scler 2006;12(5):646-51.

2. Collin, C., Davies, P., Mutiboko, I. K., & Ratcliffe, S. (2007). Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. European Journal of Neurology, 14(3), 290-296.

3. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. European Neurology 1997;38:44-48.

4. Corey-Bloom, J., Wolfson, T., Gamst, A., Jin, S., Marcotte, T. D., Bentley, H., & Gouaux, B. (2012). Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Canadian Medical Association Journal, 184(10), 1143-1150.

5. Greenberg HS, Werness SAS, Pugh JE, Andrus RO, Anderson DJ, Domino EF. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. Clinical Pharmacology and Therapeutics 1994;55:324-328.

7. Meinck HM, Schönle PWA, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. Journal of Neurology 1989;236:120-122.

8. Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. Cannabis use as described by people with multiple sclerosis. Can J Neurol Sci 2003;30(3):201-5.

9. Rog, D. J., Nurmikko, T. J., Friede, T., & Young, C. A. (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology, 65(6), 812-819.

10. Ware, M. A., Ducruet, T., & Robinson, A. R. (2006). Evaluation of herbal cannabis characteristics by medical users: a randomized trial. Harm Reduct. J,3, 32.

The treatment of cancer often includes the administration of chemotherapy and radiation, which typically result in a number of unpleasant symptoms. Patients have experienced favorable management of multiple symptoms as a result of medical marijuana therapy.

SYMPTOMS.

Medical marijuana can help cancer patients manage nausea and vomiting, pain, and loss of appetite. The potential of managing multiple symptoms makes cannabis an appealing medicine for cancer patients.

EFFECTS OF MEDICAL MARIJUANA USE.

Nausea And Vomiting (Emesis): As a natural response to the toxicity of chemotherapy treatment, nausea and vomiting result from an elevated level of a serotonin metabolite called 5-Hydroxyindoleacetic acid.[1] The elevated levels of this compound in the blood stream trigger chemoreceptors in the brain leading to nausea and vomiting. The primary action of the cannabinoids in managing nausea and vomiting is thought to cause down-regulation of the activity of chemoreceptors, which reduces the frequency and severity of emetic events.[1,2]

Evidence in favor of the use of cannabinoids in the management of emetic symptoms associated with chemotherapy has been growing since the 1980s.[2] Cannabinoids have been shown to reduce emetic events and the severity of nausea in patients undergoing chemotherapy. [2, 3] There is also evidence to suggest that medical marijuana in low doses will improve the efficacy of conventional antiemetics.[4] In addition to the management of symptoms associated with chemotherapy, clinical studies have shown cannabinoids are beneficial in the management of nausea and vomiting associated with radiation therapy and in post surgery settings.[5]

Marijuana has been shown to be particularly effective in the management of neuropathic pain associated with many conditions, including that associated with certain types of cancer.

EVIDENCE.

NAUSEA AND VOMITING (EMESIS)

1. Sharkey, K. A., Darmani, N. A., & Parker, L. A. (2014). Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. European journal of pharmacology, 722, 134-146.

2. Tramèr, M. R., Carroll, D., Campbell, F. A., Reynolds, D. J. M., Moore, R. A., & McQuay, H. J. (2001). Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ: British Medical Journal, 323(7303), 16.

3. Duran, M., Pérez, E., Abanades, S., Vidal, X., Saura, C., Majem, M., ... & Capellà, D. (2010). Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy induced nausea and vomiting.British journal of clinical pharmacology, 70(5), 656-663.

4. Parker, L. A., Rock, E. M., & Limebeer, C. L. (2011). Regulation of nausea and vomiting by cannabinoids. British journal of pharmacology, 163(7), 1411-1422.

5. Feyer, P., Jahn, F., & Jordan, K. (2013). Radiation induced nausea and vomiting. European journal of pharmacology.

THC has been shown to promote appetite and reduce wasting in patients who suffer from AIDS as well as those experiencing anorexia-cachexia as result of cancer, and cancer treatments.[6,7,8] The appetite-promoting component of medical marijuana coupled with the reduction of emetic symptoms has led many cancer patients to explore the use of cannabis to manage symptoms.

PAIN.

Marijuana has been shown to be particularly effective in the management of neuropathic pain associated with many conditions, including that associated with certain types of cancer. 9, 10 THC has a high affinity for receptors both in the central nervous system and receptors in the peripheral nervous system, which results in an analgesic effect for patients.11 One 2010 randomized control trial (RCT) on smoked cannabis concluded that a single inhalation of 25mg of cannabis containing 9.4%THC reduced the intensity of pain, improved sleep and was well tolerated by patients.12

RCTs at the University of California Center for Medicinal Cannabis Research (CMCR) consistently determined that smoked marijuana consistently led to a reduction in pain and worked in conjunction with other analgesics.11, 12, 13 The analgesic properties of marijuana are strongly supported for the management of chronic neuropathic pain. 12, 13

ANOREXIA AND CACHEXIA

6. Brisbois, T. D., de Kock, I. H., Watanabe, S. M., Mirhosseini, M., Lamoureux, D. C., Chasen, M., ... & Wismer, W. V. (2011). Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Annals of oncology,22(9), 2086-2093.

7. Johannigman, S., & Eschiti, V. (2013). Medical Use of Marijuana in Palliative Care. Clinical journal of oncology nursing, 17(4), 360-362.

8.Strasser, F., Luftner, D., Possinger, K., Ernst, G., Ruhstaller, T., Meissner, W., & Cerny, T. (2006). 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.Journal of Clinical Oncology, 24(21), 3394-3400.

PAIN

9. Grant, I., Atkinson, J. H., Gouaux, B., & Wilsey, B. (2012). Medical marijuana: clearing away the smoke. The open neurology journal, 6, 18.

10. Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D., Potts, R., & Fallon, M. T. (2010). 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.Journal of pain and symptom management, 39(2), 167-179.

11. Noyes, R., Brunk, S. F., Avery, D. A., & Canter, A. C. (1975). The analgesic properties of delta-9-tetrahydrocannabinol. Clin Pharmacol Ther, 18(1), 84-89.

12. Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., ... & Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal, 182(14), E694-E701.

13. Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., & Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. The Journal of Pain, 9(6), 506-521.

EVIDENCE.

1. Corral, V. L. (2001). Differential effects of medical marijuana based on strain and route of administration: A three-year observational study. Journal of Cannabis Therapeutics, 1(3-4), 43-59.

2. Cunha, J. M., Carlini, E. A., Pereira, A. E., Ramos, O. L., Pimentel, C., Gagliardi, R., ... & Mechoulam, R. (1980). Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology, 21(3), 175-185.

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Epilepsy encompasses a collection of neurological disorders, which cause varying forms of seizures ranging from nearly undetectable to vigorous and violent whole body convulsions. The immediate cause of the seizures is unknown in most cases, although seizures can be caused by primary conditions like epilepsy, as well as trauma, stroke, brain cancer, and substance abuse.

SYMPTOMS.

Seizures are the main symptom of epilepsy and are classified into six main types: clonic, tonic, tonic-clonic, myoclonic, absence and atonic seizures. Although the severity and characteristics of each seizure type varies, each is accompanied by a loss of consciousness. In addition to seizures, there is typically a refractory period of disorientation after an episode referred to as the postictal period.

EFFECTS OF MEDICAL MARIJUANA USE.

Cannabidiol (CBD) is the primary cannabinoid associated with therapeutic management of epilepsy.[1, 2] CBD was provided to patients whose epileptic symptoms were unaffected by conventional medications in the context of a randomized control trial, resulting in a marked improvement in symptom presentation.[2, 3] Evidence for the use of cannabis in the management of epilepsy is limited. However, anecdotal reports of success have led some patients and physicians to explore the use of cannabis when conventional treatments have proven unsuccessful.

Glaucoma presents in two main forms, open-angle glaucoma and closed-angle glaucoma. The condition is the result of increased pressure within eye causing pressure to be exerted on the optic nerve obscuring vision. Medical marijuana has been a recognized therapy for the management of glaucoma since the 1970s.[1,2]

SYMPTOMS.

Open-angle glaucoma accounts for the majority of cases and is characterized by silent, progressive loss of the visual field without any acute pain, as a result of progressive damage to the optic nerve.

Closed-angle glaucoma is characterized by the sudden onset of ocular pain, decreased vision, visual halos, conjunctivitis, and high intraocular pressure. Symptoms of nausea, vomiting, and abnormal pupil shape and size are also commonly reported.

EFFECTS OF MEDICAL MARIJUANA USE.

Intraocular Pressure: Newer and more effective medications exist to treat glaucoma, but there have been studies examining the effects of medical marijuana on both glaucoma patients and healthy patients have consistently demonstrated a reduction of 25-30% in intraocular pressure[1, 2, 3] Occasionally the reduction in pressure has been as high as 50%[4] The reduction in pressure typically lasts between 2 and 4 hours.[3] Post mortem examination of glaucoma patients has detected decreased levels of endocannabinoids suggesting that regulation of intraocular pressure by medical marijuana may be through endocannabinoid receptors in ocular tissues.[5] The exact reason for the reduction in intraocular pressure as a result of medical marijuana use is undetermined.

Pain: The management of pain resulting from closed-angle glaucoma has not been specifically evaluated in clinical studies. Nevertheless, cannabinoids are a proven analgesic and have demonstrated efficacy in a wide variety of chronic pain conditions.

EVIDENCE.

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4. Russo, E., Mathre, M. L., Byrne, A., Velin, R., Bach, P. J., Sanchez-Ramos, J., & Kirlin, K. A. (2002). Chronic cannabis use in the compassionate investigational new drug program: An examination of benefits and adverse effects of legal clinical cannabis. Journal of Cannabis Therapeutics, 2(1), 3-57.

5. Chen, J., Matias, I., Dinh, T., Lu, T. and others. (2005). Finding of endocannabinoids in human eye tissues: implications for glaucoma. Biochem.Biophys.Res.Commun. 330: 1062-1067.

TWEED GROW ROOM #6

CANNABIS AND THE CANNABINOIDS

Key Points extracted from Health Canada's
Cannabis Information for Health Care Professionals.

WHAT'S INSIDE:

http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php is the link to the comprehensive Health Canada document entitled Information for Health Care Professionals: Cannabis and the Cannabinoids for overall reference. The references noted in this article can be found starting on page 95 of the document for review as needed.

Health Canada has gone to great lengths to provide a comprehensive analysis of the makeup, pharmacology, uses, and evidence for all types of medical marijuana as part of the switchover in guidelines from MMAR to MMPR. The document reference above is incredibly detailed and is a very interesting and in some ways challenging read due to the degree of detail it provides. Other references have well covered the main components of organic marijuana and have referenced the various conditions for which this medicine is believed to work.

What follows here is a compilation of the most salient points of evidence for many conditions that marijuana is commonly used, occasionally used, some where its use or utility is lesser known, and some where its use is less or not advisable. In some cases, sections are summarized, but in most cases, the language is taken exactly from the Health Canada document because this provides the most clear and precise language and avoids editorializing.

Before beginning, it is noted that the document is able to provide far more evidence references for pill and spray based THC products such as Marinol (drorabinol), Cesament (nabilone), and Sativex. Reasons differ slightly based on indication, but the main reason for more science on these products is that they are easier to study and provide a true placebo group while blinding participants and investigators from knowing what they are taking in. This has been a challenge with smoked or vaporized THC products to the unique odour and taste of the product. Thus, this document will focus on evidence for the use of smoked marijuana but will reference evidence in pill/spray products particularly when there is less evidence for smoked marijuana. It is up to the practitioner to decide if there is, as it seems clear that there is, a clear correlation between the efficacy of the pill/spray products and the smoked/vaporized product.

Hereafter we address each sub-section, which pertains to the clinical use of cannabis in the Health Canada document (the focus of Section 4 in the document).

4.1 PALLIATIVE CARE.

This section references the fact that treatment in palliative care is a mixture of treating various symptoms and side effects of a particular end of life condition and the treatment associated therewith.

"These include intractable nausea and vomiting associated with chemotherapy or radiotherapy, anorexia/cachexia, severe intractable pain, severe depressed mood, and insomnia[173,174]. The use of cannabinoids for palliative care may also result in a decrease in the number of medications used by this patient population."[173]

Specific symptomatology will be addressed with each section as they are addressed in the health Canada report.

4.2 NAUSEA AND VOMITING.

"Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing and common adverse events associated with cancer treatment[50]. While chemotherapy-induced vomiting generally appears to be well-controlled with current first-line therapies, the associated acute, delayed, or anticipatory nausea remain more poorly controlled and the use of cannabis/cannabinoids may provide some measure of benefit in certain cases[11,37]. It is important to note that excessive use of cannabis has been reported to paradoxically trigger a chronic cyclic vomiting syndrome (i.e. hyperemesis)"

and

"Patient claims that smoked cannabis relieves CINV are widely recognized, and increasing evidence suggests a role for the endocannabinoid system in the regulation of nausea and vomiting[11]. Cannabinoid CB1 and CB2 receptors have been found in areas of the brainstem associated with emetogenic control[51,52], and results from animal studies suggest the anti-nausea and anti-emetic properties of cannabinoids (e.g. Δ9-THC, dronabinol, nabilone) are most likely related to their agonistic actions at CB1 receptors[9,11,53]. An in vivo animal study and one small clinical study 36 have also suggested Δ8-THC to be a more potent anti-emetic than Δ9-THC."[9,10]

and

"While no peer-reviewed clinical trials of smoked cannabis for the treatment of CINV exist, Musty and Rossi have published a review of U.S. state clinical trials on the subject[36]. Patients who smoked cannabis showed a 70 - 100% relief from nausea and vomiting, while those who used a Δ9-THC capsule experienced 76 - 88% relief[36]. Plasma levels of > 10 ng/mL Δ9-THC were associated with the greatest suppression of nausea and vomiting, although levels ranging between 5 and 10 ng/mL were also effective[36]. In all cases, patients were admitted only after they failed treatment with standard phenothiazine anti-emetics. A small clinical trial comparing smoked cannabis (2.11% Δ9-THC, in doses of 8.4 mg or 16.9 mg Δ9-THC; 0.30% cannabinol; 0.05% cannabidiol) to ondansetron (8 mg) in ipecac-induced nausea and vomiting in healthy volunteers showed that both doses of Δ9-THC reduced subjective ratings of queasiness and objective measures of vomiting; however, the effects were very modest compared to ondansetron[37]. Furthermore, only cannabis produced changes in mood and subjective state."

4.3 WASTING SYNDROME.

"The ability of cannabis to increase appetite has been recognized anecdotally for many years[40]. In addition, results from epidemiological studies suggest that people actively using cannabis have higher intakes of energy and nutrients than non-users[56]. Controlled laboratory studies with healthy subjects suggest exposure to cannabis, whether by inhalation or oral ingestion of Δ9-THC-containing capsules, correlates positively with an increase in food consumption, caloric intake, and body weight[39,40]. Studies showing a high concentration of CB1 receptors in brain areas associated with control of food intake and satiety lend further support to the link between cannabis consumption and appetite regulation[57,58,59]. Furthermore, increasing evidence suggests a role for the endocannabinoid system not only in modulating appetite, food palatability, and intake, but also in energy metabolism and the modulation of both lipid and glucose metabolism (reviewed in."[1,58,59,60]

This has been demonstrated specifically in HIV patients to stimulate appetite and weight gain as evidenced in:
"One study[26] showed that experienced HIV+ cannabis smokers with clinically significant muscle mass loss benefited from both dronabinol (four to eight times the standard 2.5 mg Δ9-THC b.i.d dose, or 10 - 20 mg Δ9-THC daily, three times per week for a total of eight sessions) and smoked cannabis (three puffs at 40 sec intervals; ~800 mg cigarettes containing 1.8 - 3.9% THC giving an estimated total daily amount of 14.4 mg - 31.2 mg THC in the cigarette, three times per week, for a total of eight study sessions). A subsequent study employed even higher doses of dronabinol (20 - 40 mg total Δ9-THC daily, for a total of four days) and smoked cannabis (~800 mg cannabis cigarettes containing 2 and 3.0% THC, administered four times per day, giving an estimated 64 - 125 mg total Δ9-THC daily in the cigarette, for a total of four days)[27]. Both drugs produced substantial and comparable increases in food intake and body weight, as well as improvements in mood and sleep."[26,27]

4.3.2 TO STIMULATE APPETITE AND PRODUCE WEIGHT GAIN IN CANCER PATIENTS.

The effects in cancer patients are best encapsulated here:
"...While it is anecdotally known that smoking cannabis

can stimulate appetite, the effects of smoking cannabis on appetite and weight gain in patients with cancer cachexia have not been studied. The results from trials with oral Δ9-THC (dronabinol) or 38 oral cannabis extract are mixed and the effects, if any, appear to be modest. In two early studies, oral THC (dronabinol) improved appetite and food intake in some patients undergoing cancer chemotherapy[61,62]. An open-label study of dronabinol (2.5 mg Δ9-THC, two to three times daily, four to six weeks) in patients with unresectable or advanced cancer reported increases in appetite and food intake, but weight gain was only achieved in a few patients[63,64]. Modest weight gain was obtained with a larger dosing regimen of dronabinol (5 mg t.i.d.), but the CNS side effects including dizziness and somnolence were limiting factors." [65]

4.3.3 ANOREXIA NERVOSA.

This section is best summarized by the following:
"The endocannabinoid system has been implicated in appetite regulation and is suspected to play a role in eating disorders such as anorexia nervosa[58,66]. However, genetic studies have thus far failed to agree on an association between genes coding for endocannabinoid system proteins and the manifestation of anorexia nervosa, in spite of epidemiological and familial studies which suggest a genetic basis for this disorder." [67,68]

and

"No studies have examined the effects of smoking cannabis on anorexia nervosa. Both the British Medical Association[13] and the Institute of Medicine[54] concluded that cannabis was unlikely to be effective in patients with anorexia nervosa; however, further research may be warranted."

4.4.1 MULTIPLE SCLEROSIS.

This section is best summarized by:
"A number of studies, both in patients suffering from multiple sclerosis (MS) and in animal models of the disease, suggest the disorder is associated with changes in endocannabinoid levels, although the findings are conflicting ."[69,70,71,72]

and

"Historical and survey data in humans, published reports spanning 100 years suggest that people with spasticity (one of the symptoms associated with MS) may experience relief with cannabis[73]. In the UK, 43% of patients with MS reported having experimented with cannabis at some point, and 68% of this population used it to alleviate the symptoms of MS[74]. In Canada, the prevalence of medicinal use of cannabis among patients seeking treatment for MS, in the year 2000, was reported to be 16% in Alberta, with 43% of study respondents stating they had used cannabis at some point in their lives[24]. Fourteen percent of people with MS surveyed in the year 2002 in Nova Scotia reported using cannabis for medical purposes, with 36% reporting ever having used cannabis for any purpose[25]. MS patients reported using cannabis to manage symptoms such as spasticity and chronic pain as well as anxiety and/or depression[24,25]. MS patients also reported improvements in sleep. Reputed dosages of smoked cannabis by these patients varied from a few puffs to 1 g or more at a time."[25]

and

Clinical studies with smoked cannabis:
"There has only been one clinical study so far using smoked cannabis for symptoms associated with MS [34]. The study, a double-blind, placebo-controlled, crossover trial reported a statistically significant reduction in patient scores on the modified Ashworth scale for measuring spasticity after patients smoked cannabis once daily for three days (each cigarette contained 800 mg of 4% Δ9-THC; total available Δ9-THC dose of 32 mg per cigarette.)[34] Smoking cannabis was also associated with a statistically significant reduction in patient scores on the visual analog scale for pain, although patients reportedly had low levels of pain to begin with[34]. No differences between placebo and cannabis were observed in the timed-walk task, a measure of physical performance[34]. Cognitive function, as assessed by the Paced Auditory Serial Addition Test (PASAT), appeared to be significantly decreased immediately following administration of cannabis; however, the long-term clinical significance of this finding was not examined in this study[34]. The majority of patients (70%) were on disease-modifying therapy (e.g. interferon ß-1a, interferon ß-1b, or glatiramer), and 60% were taking anti-42 spasticity agents (e.g. baclofen or tizanidine). Cannabis treatment was associated with a number of different, but commonly observed adverse effects including dizziness, headache, fatigue, nausea, feeling – too high, and throat irritation[34]. Study limitations included the fact that the majority of patients had prior experience with cannabis, and that the study was unblinded since most of the patients were able to tell apart the placebo from the active treatment with cannabis."[34]

4.4.2 AMYOTROPHIC LATERAL SCLEROSIS.

"There is limited evidence that cannabinoids have a role in modulating ALS[77,78], and two trial offers mixed results with oral agents only."[79,80]

4.4.3 SPINAL CORD INJURY (OR SPINAL CORD DISEASE).

"Pre-clinical animal studies suggest that spinal cord injury triggers changes in the activity of the endocannabinoid system, and that cannabinoid receptor agonists may alleviate neuropathic pain associated with spinal cord injury [81,82,83]. However, limited clinical information exists regarding the use of cannabinoids to treat symptoms associated

with spinal cord injury such as pain, spasticity, muscle spasms, urinary incontinence, and difficulties sleeping."

and

"No clinical trials of smoked cannabis for the treatment of these symptoms have been documented, but subjective improvements have been anecdotally reported by patients smoking cannabis[54,84]. Double-blind, crossover, placebo-controlled studies of oral Δ9-THC and/or Δ9-THC : CBD extract (Sativex®) suggested modest improvements in pain, spasticity, muscle spasms, and sleep quality in patients with spinal cord injury ."[54,85,86]

4.5 EPILEPSY.

"Increasing evidence points to a role for the endocannabinoid system in the modulation of neuronal tone and excitability, and possibly in epilepsy. Human and animal studies suggest epileptic activity is associated with changes in the levels and distribution of CB^1 receptors in the hippocampus[87,88,89]. Reduced levels of the endocannabinoid anandamide have been detected in the cerebrospinal fluid of patients with untreated, newly diagnosed, temporal lobe epilepsy." [90]

4.6 PAIN.

"It is now well established that the endocannabinoid system plays an important role in the modulation of pain states and that elements of the endocannabinoid system can be found at supraspinal, spinal, and peripheral levels of pain pathways [3,91]. The particular distribution of cannabinoid receptors provides an anatomical basis to explain some of the analgesic effects of cannabinoids, and a number of pre-clinical studies suggest a functional role for endocannabinoids (such as anandamide and 2-arachidonoylglycerol (i.e. 2-AG)) in suppressing pain under physiological conditions." [3]

and

"However, results from both experimental models of pain in human volunteers and from clinical trials of patients suffering from pain instead suggest cannabinoids may be more effective for chronic rather than acute pain."[92,93, 169]

and

Patient/study subject population:

"Many, if not most, of the clinical trials of cannabinoids for the treatment of pain (and even other disorders such as multiple sclerosis) have recruited patients or volunteers who have had prior exposure or experience with cannabis or cannabinoids. This has raised the issue of unblinding because any study subjects having prior experience with cannabis or cannabinoids would be more likely to be able to distinguish active treatment with these drugs from the placebo control." [170]

4.6.1.1 EXPERIMENTALLY-INDUCED ACUTE PAIN.

Pre-clinical studies:

"A number of pre-clinical studies suggest that anandamide, THC, and certain synthetic cannabinoids block pain responses in different animal models of acute pain (reviewed in[2,94].) Cannabinergic modulation of neuronal circuits in the brain and spinal cord can inhibit nociceptive processing[95,96,97,171]. However, despite the results obtained in pre-clinical studies, the results of studies using cannabis or cannabinoids (e.g. nabilone) to alleviate experimentally-induced acute pain in humans are mixed."

and

"Clinical studies with smoked cannabis showed, at best mixed results."[32,33,98,99]

4.6.1.2 POST-OPERATIVE PAIN.

Summary:

Cannabinoids do not appear to be effective in treating post-operative pain.[100,101,102,103]

4.6.2.2 NEUROPATHIC PAIN OR CHRONIC NON-CANCER PAIN.

Neuropathic pain:

The benefits of cannabis for neuropathic pain are among the best described and studied and are summarized here:

"Short-term clinical studies suggest prescription cannabinoid medications (e.g. nabiximols, dronabinol, nabilone) are moderately effective in reducing intractable central or peripheral neuropathic pain of various etiologies in individuals already receiving analgesic drugs [105]. Side effects appear to be comparable to existing treatments and typically include dizziness/lightheadedness, sedation, confusion, ataxia, a feeling of intoxication, euphoria (high), xerostomia, dysgeusia, and hunger[105,106]. These effects may be minimized by employing low doses of cannabinoids that are gradually escalated, as required. The following summarizes the existing clinical information on the use of cannabis and cannabinoids (THC, nabilone, dronabinol and nabiximols) to treat neuropathic and chronic non-cancer pain."

This section offers multiple study examples with smoke cannabis, a couple of examples of which are noted here:

"Clinical studies with smoked or vapourized cannabis
A randomized, double-blind, placebo-controlled, cross-over study of cannabis-experienced patients suffering from chronic neuropathic pain of various etiologies (complex regional pain syndrome, central "neuropathic pain from spinal cord injury or multiple sclerosis, or peripheral neuropathic pain from diabetes or nerve injury) reported that administration of either a low dose or a high dose of smoked cannabis (3.5% Δ9-THC, 19 mg total available Δ9-THC; or 7% Δ9-THC, 34 mg total available Δ9-THC) was associated with significant equianalgesic decreases

in central and peripheral neuropathic pain[28]. No analgesic effect was observed in tests of experimentally-induced pain (tactile or heat stimuli). Patients were taking other pain control medications during the trial such as opioids, anti-depressants, non-steroidal anti-inflammatory drugs, or anti-convulsants. Adverse effects associated with the use of cannabis appeared to be dose-dependent and included feeling high, sedation, confusion, and neurocognitive impairment. Cognitive changes appeared to be more pronounced with higher doses of Δ9-THC[28]."

and

"In another randomized, placebo-controlled study a greater than 30% decrease in HIV-associated sensory neuropathic pain was reported in 52% of cannabis-experienced patients smoking cannabis cigarettes containing 3.56% Δ9-THC (32 mg total available Δ9-THC per cigarette), three times per day (96 mg total daily amount of Δ9-THC) for five days, compared to a 24% decrease in pain in the placebo group[18]. The number of patients that needed to be treated (NNT) to observe a 30% reduction in pain compared to controls was 3.6 and was comparable to that reported for other analgesics in the treatment of chronic neuropathic pain. In the experimentally-induced pain portion of the study, smoked cannabis was not associated with a statistically significant difference in acute heat pain threshold compared to placebo. However, it did appear to reduce the area of heat and capsaicin-induced acute secondary hyperalgesia[18]. Patients were taking other pain control medications during the trial such as opioids, gabapentin or other drugs. Adverse effects of smoked cannabis in this study included sedation, dizziness, confusion, anxiety, and disorientation."

Multiple examples of trials showing the benefits of oral and vaporized products in neuropathic pain follow in this section:
"According to the consensus statement and clinical guidelines on the pharmacological management of chronic neuropathic pain published by the Canadian Pain Society in 2007, the Society considered cannabinoid-based therapies (e.g. dronabinol and nabiximols) to be fourth-line treatments for neuropathic pain, mostly as adjuvant analgesics for pain conditions refractory to standard drugs[108] (but also see section 4.7.3 and reference[506] for updated clinical guidelines on the use of cannabinoids for the treatment of symptoms associated with fibromyalgia). Health Canada has approved Sativex® (with conditions) as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis."[45]

and

"A Canadian systematic review of randomized clinical trials of cannabinoids (cannabis, nabilone, dronabinol and nabiximols) for the treatment of chronic non-cancer pain (neuropathic pain, mixed chronic pain, rheumatoid arthritis, fibromyalgia) concluded that cannabinoids are modestly effective for neuropathic pain, with preliminary evidence of efficacy in rheumatoid arthritis (see section 4.7.2) and fibromyalgia (see section 4.7.3)[30]. Major limitations identified in the review were short trial duration, small sample sizes, and modest effect sizes, with a need for larger trials of longer duration to better establish efficacy and safety as well as potential for abuse."

4.6.2.3 CANCER PAIN.

Two studies show benefits in cancer related pain from marinol[109,110], while the results with Sativex are mixed, with two studies showing benefits[12,111] and the other showing mixed results.[47]

Opiate sparing effects

"Opioid-sparing" effects and cannabinoid-opioid synergy
The opioid-sparing effect refers to the ability of a non-opioid medication to confer adjunctive analgesia with the use of a lower dose of the opioid thereby decreasing opioid-associated side effects. While there are some pre-clinical data supporting such an effect for cannabinoids, this is less well-established in published clinical studies. The following information summarizes the results from pre-clinical and clinical studies investigating cannabinoid-opioid interactions and the potential opioid-sparing effect of cannabinoids."

The relevant studies can be noted in this section.

4.6.2.4 HEADACHE AND MIGRAINE.

"While historical and anecdotal evidence suggest a role for cannabis in the treatment of headache and migraine[114], no controlled clinical studies of cannabis or prescription cannabinoids to treat headache or migraine have been carried out to date."[115,116]

4.7. ARTHRITIS AND MUSCULOSKELETAL DISORDERS.

"...While scientific studies have demonstrated that joints, bone, and muscle all contain a working endocannabinoid system[6,7,8], there is relatively little scientific or medical information on the use of cannabis or cannabinoids to treat either the arthritides or musculoskeletal disorders. The available information is summarized below."

Osteoarthritis

"Very little information is available regarding the use of cannabis or cannabinoids to treat osteoarthritis. One study reported elevated levels of the endocannabinoids anandamide and 2-arachidonoylglycerol (i.e. 2-AG), and the entourage compounds PEA and OEA in the spinal cords of rats with experimentally-induced knee joint osteoarthritis."[117]

Rheumatoid Arthritis

"A preliminary clinical study assessing the effectiveness of nabiximols (Sativex®) for pain caused by rheumatoid arthritis reported a modest but statistically significant analgesic effect on movement and at rest, as well as improvement in

quality of sleep[42]. Administration of nabiximols was well tolerated and no significant toxicity was observed. The mean daily dose in the final treatment week was 5.4 pump actuations (equivalent to 14.6 mg THC and 13.5 mg CBD/day, treatment duration was three weeks)[42]. The differences observed were small and variable across the participants."

and

"...the current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana for those patients experiencing severe pain associated with severe arthritis who have either not benefited from, or would not be considered to benefit from, conventional treatments." [384]

Fibromyalgia

Clinical studies with smoked or orally ingested cannabis:
"There are no clinical trials of smoked or ingested cannabis for the treatment of fibromyalgia. However, a cross-sectional survey of 291 patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis) reported that one of the reasons patients used cannabis was to improve sleep[22]. A two-week, randomized, double-blind, placebo-controlled, cross-over study of patients suffering from chronic neuropathic pain reported that those who smoked 25 mg of cannabis containing 9.4% Δ9-THC, three times per day for five days (2.35 mg total available Δ9-THC per cigarette, or 7.05 mg total Δ9-THC per day), fell asleep more easily and more quickly, and experienced fewer periods of wakefulness."[29]

And reference to current guidelines:
"The recently published Canadian Clinical Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome (endorsed by the Canadian Pain Society and the Canadian Rheumatology Association) indicate that with regards to possible treatments, a trial of a prescribed pharmacologic cannabinoid may be considered in a patient with fibromyalgia, particularly in the setting of important sleep disturbance (this recommendation was based on Level 3, Grade C evidence)[108]. For additional information regarding the use of cannabis/cannabinoids to alleviate sleep disorders or disturbances, please consult section 4.8.5.2."

4.7.4 OSTEOPOROSIS.

"....While increasing evidence suggests a role for the endocannabinoid system in bone homeostasis, the role of cannabinoids in the treatment of osteoporosis has only been studied pre-clinically and the information remains unclear due to the complex and conflicting results among the various pre-clinical studies."

4.8 OTHER DISEASES AND SYMPTOMS.

4.8.1 MOVEMENT DISORDERS.

"The individual components of the endocannabinoid system are particularly abundant in areas of the brain which control movement, such as the basal ganglia[118]. Motor effects generally arise as a consequence of changes in endocannabinoid system activity, with activation of the CB1 receptor typically resulting in inhibition of movement[118]. A number of studies have reported changes in CB1 receptor levels and CB1 receptor activity in motor diseases such as Parkinson's and Huntington's disease[119,120,121,122], and the findings from such studies suggest a role for the endocannabinoid system in the pathophysiology of these and other neurological diseases."

4.8.2 GLAUCOMA.

"Ocular (as well as systemic) administration of cannabinoids typically lowers IOP by up to 30% (see [44] for a full reference list). How cannabinoids reduce IOP is unclear, but several possible mechanisms have been proposed including reduction of capillary pressure, decreased aqueous humour production, and improved aqueous humour uveoscleral outflow and outflow facility."[123,124,125,126,127]

Several studies show benefit, but some evidence of a rise in IOP with cannabidiol:
"A well-controlled pilot study of six patients with ocular hypertension or early primary open-angle glaucoma reported that single sub-lingual doses of 5 mg Δ9-THC (applied by means of an oro-mucosal spray) significantly but temporarily reduced IOP 2 h after administration[43]. A single sub-lingual dose of 20 mg cannabidiol (CBD) (containing ~ 1 mg Δ9-THC) had no effect, while a single sub-lingual dose 40 mg of CBD (containing ~ 2 mg Δ9-THC) caused a significant transient increase in IOP 4 h after administration[43]. A non-randomized, unmasked, uncontrolled clinical study reported some improvement in IOP after oral ingestion of Δ9-THC (2.5 or 5 mg q.i.d., up to a maximum of 20 mg/day; treatment duration range 3 - 36 weeks) in patients with end-stage, open-angle glaucoma not responsive to medications or surgery[128]. Some patients appeared to develop tolerance to the intra-ocular pressure-lowering effects of Δ9-THC, and almost half discontinued treatment due to Δ9-THC-associated toxicity (e.g. dizziness, dry mouth, sleepiness, depression, confusion)[128]. Aside from lowering IOP, cannabinoids such as Δ9-THC and CBD may also have neuroprotective effects which could also be useful in the management of glaucoma[44,129,130,131,132,133,134,135,136,137,138]. Results from a survey carried out among 1 516 glaucoma patients at tertiary glaucoma clinics in Toronto and Montreal suggested that approximately 13% of these patients claimed they used complementary and alternative medicines to treat glaucoma, and from among these patients 2.3% reported using cannabis to treat their glaucoma."[139]

4.8.3 ASTHMA.

THC has been shown to have a bronchodilatory effect which may be beneficial but this must be weighed against the effects of smoking. Other delivery mechanisms are being explored and may show some benefit if properly explored.

4.8.4 HYPERTENSION.

"CB1 receptors are expressed on various peripheral tissues including the heart and vasculature, and cannabinoid agonists and endocannabinoids decrease arterial blood pressure and cardiac contractility (reviewed in)."[140]

There is no clear evidence on the clinical efficacy of cannabis for hypertension.

4.8.5 PSYCHIATRIC DISORDERS.

"There are anecdotal and, in some cases, historical claims regarding the beneficial effects of cannabis and cannabinoids in the treatment of a variety of psychiatric disorders including anxiety, depression, sleep disorders, post-traumatic stress disorder, and withdrawal symptoms associated with drug abuse/addiction. The following sections provide information gathered from the scientific and medical literature regarding the use of cannabis and cannabinoids in the treatment of such disorders."

4.8.5.1 ANXIETY AND DEPRESSION.

"Long-term cannabis users report reductions in anxiety, increased relaxation, and relief from tension[21]. One survey conducted among over 4 400 respondents suggested that those who consumed cannabis daily or weekly reported a decrease in depressed mood, and an increase in positive affect, compared to respondents who claimed they never consumed cannabis[141]. However, the study suffered from a number of serious drawbacks and should be interpreted with this in mind."

Clinical data for cannabis and THC:

"While the routine use of cannabis or prescription cannabinoid medications to treat primary anxiety or depression should be viewed with caution, and especially discouraged in patients with a history of psychotic disorders (see section 7.7.3.3), limited clinical evidence indicates that these drugs may present alternative therapeutic avenues in patients suffering from anxiety or depression secondary to certain chronic diseases." See studies 38 and 175.

Cannabidiol:

"Increasing evidence suggests a role for cannabidiol (CBD) in decreasing anxiety, although the extent to which CBD (at the concentrations commonly found in cannabis) is able to achieve this effect remains uncertain."[31,142]

4.8.5.2 SLEEP DISORDERS.

Clinical data:

"A number of clinical studies point to a potential beneficial role for smoked cannabis or prescription cannabinoids (dronabinol, nabilone, nabiximols) in the treatment of sleep difficulties or disturbances associated with chronic pain (cancer pain, chronic non-cancer pain, diabetic peripheral neuropathy), HIV-associated anorexia-cachexia, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury, rheumatoid arthritis, fibromyalgia, inflammatory bowel disease, multiple sclerosis-associated bladder dysfunction, post-traumatic stress disorder, and chemosensory alterations and anorexia-cachexia associated with advanced cancer[22,23,25,26,27,29,38,42,48,49,54,75,76,80,85,86,104,108,170]. In most of these studies, the effect on sleep was measured as a secondary outcome. Although presented elsewhere throughout the text in the relevant sections, brief summaries of these studies are presented below."

and

Smoked cannabis:

"Surveys carried out among patients suffering from multiple sclerosis reported cannabis-associated improvements in sleep in this patient population[24,25]. Reported dosages of smoked cannabis varied from a few puffs, to 1 g or more, at a time[24]. A cross-sectional survey of patients suffering from fibromyalgia reported that subjects claimed using cannabis (by smoking and/or eating) for a variety of symptoms associated with fibromyalgia, including sleep disturbance[23]. A cross-sectional survey of 291 patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis) reported that one of the reasons patients used cannabis was to improve sleep[22]. A two-week, randomized, double-blind, placebo-controlled, cross-over study of patients suffering from chronic neuropathic pain reported that those who smoked 25 mg of cannabis containing 9.4% Δ9-THC, three times per day for five days (2.35 mg total available Δ9-THC per cigarette, or 7.05 mg total Δ9-THC per day), fell asleep more easily and more quickly, and experienced fewer periods of wakefulness."[29]

NOTE: Discontinuation of THC use in very heavy smokers may cause sleep problems.

4.8.5.3 POST-TRAUMATIC STRESS DISORDER (PTSD).

Clinical data:

"Although anecdotal evidence suggests a role for cannabis in the management of PTSD symptoms, no properly controlled clinical trials on this topic exist. In fact the only clinical trial reported to date examining the effect of cannabinoids in PTSD is an open-label, non-placebo-controlled trial of nabilone for PTSD[41]. Forty-seven patients diagnosed with PTSD (according to DSM-IV-TR criteria), having at least a two-year history of PTSD-related nightmares refractory to conventional therapies, a minimum of once weekly nightmares, and with no prior history of sensitivity to cannabinoids or evidence of psychotic reactions, were admitted into the study. Patients did not discontinue any concomitant psychotropic medications, and were started on 0.5 mg nabilone, 1 h prior to bedtime. All doses were kept below 6 mg daily. The effective dose range varied between 0.2 mg and 4 mg nightly. Seventy-two percent of

patients self-reported total cessation or lessening of severity of nightmares (treatment duration 4 - 12 months or longer). Other self-reported benefits included an improvement in sleep time, a reduction in daytime flashbacks, and cessation of night sweats. Reported side effects included light-headedness, amnesia, dizziness, and headache. No tolerance to nabilone was observed in this clinical trial."

4.8.5.4 ALCOHOL AND OPIOID WITHDRAWAL SYMPTOMS (DRUG WITHDRAWAL SYMPTOMS).

Alcohol

"There is evidence to suggest complex functional interactions between ethanol and the endocannabinoid system."[172]

Opioids

"Anecdotal information and findings from some animal studies suggest that cannabinoids might be useful in treating the symptoms associated with opioid withdrawal [113,143,144,145,146], but there are no supporting clinical studies in this regard. The overlapping neuroanatomical distribution, convergent neurochemical mechanisms, and comparable functional neurobiological properties of the cannabinoid and opioid systems may help explain why cannabinoids could substitute for opioids to potentially alleviate withdrawal symptoms associated with opioid abstinence[112]. However, further research is required on this subject."

4.8.5.5 SCHIZOPHRENIA AND PSYCHOSIS.

Cannabis/THC and psychosis

"Regardless of which hypothesis is correct, there is much scientific evidence to suggest a positive association between cannabis use and the development of psychosis, especially in people susceptible to psychotic disorders but also in adolescents[14,15,17,19,20]. Furthermore, controlled clinical studies carried out in those with no history of psychotic disorders reported the manifestation of transient schizophrenia-like symptoms induced by the intravenous administration of Δ9-THC.[16] Likewise, intravenous administration of Δ9-THC in schizophrenics was associated with transient exacerbation of core psychotic symptoms."[15]

and

"The findings presented above and in section 7.7.3 suggest that cannabis use, as well as exposure to Δ9-THC alone, would not be beneficial, and in fact would actually be harmful to those who may be suffering from psychotic disorders, or who may have a genetic predisposition or family history of psychosis or schizophrenia."

and

Cannabidiol

"A number of pre-clinical and clinical studies have suggested that, in contrast to THC, other cannabinoids such as cannabidiol (CBD) may in fact have anti-psychotic properties and may benefit psychotic patients."[147,148]

and

"In conclusion, consumption of cannabis or other psychoactive cannabinoids (e.g. dronabinol, nabilone) should be treated with considerable caution in this patient population as these substances are believed to trigger psychotic episodes, lower the age of onset of symptoms, and contribute to a negative long-term prognosis in vulnerable individuals. Additionally, the therapeutic potential of CBD alone in the treatment of schizophrenia/psychosis, while promising, requires further study."

4.8.6 ALZHEIMER'S DISEASE AND DEMENTIA.

While still controversial, a widely accepted theory underlying the pathophysiology of Alzheimer's disease (AD) is the deposition of amyloid- (A) protein in specific brain regions leading to localized neuroinflammatory responses and accumulation of intra-cellular neurofibrillary tangles (composed of hyperphosphorylated tau protein); these events result in neuronal cell death with accompanying loss of functional synapses and changes in neurotransmitter levels[149]. These pathological processes are thought to give rise to disease-associated symptoms such as memory deficits, and cognitive and motor impairments.[149]

and

"The endocannabinoid system and Alzheimer's disease There is some evidence to suggest a role for the endocannabinoid system in the pathophysiology of AD."[149,150]

and

"A Cochrane database systematic review of cannabinoids for the treatment of dementia concluded that there was insufficient clinical evidence to suggest cannabinoids as being effective in the improvement of disturbed behavior in dementia or in the treatment of other symptoms of dementia." [151]

4.8.7 INFLAMMATION.

The role of the endocannabinoid system in inflammation is complex as the endocannabinoid system has been implicated in both pro- and anti-inflammatory processes."[150]

"Therefore, while it is possible that some cannabinoids (e.g. HU-210) may have therapeutic value in the treatment of certain inflammatory skin conditions (such as psoriasis, pruritus, and dermatitis), it is also possible for some cannabinoids to trigger adverse skin reactions. Much further research is required in this area."

4.8.8 GASTROINTESTINAL SYSTEM DISORDERS (IRRITABLE BOWEL SYNDROME, INFLAMMATORY BOWEL DISEASE, HEPATITIS, PANCREATITIS, METABOLIC SYNDROME/OBESITY).

"Historical and anecdotal reports suggest that cannabis has been used to treat a variety of gastrointestinal disorders (e.g. diarrhea, inflammation, and pain of gastrointestinal origin)." [152,153,154]

4.8.8.1 IRRITABLE BOWEL SYNDROME.

NOTE: There is no convincing evidence that cannabis has a helpful role in IBS and the studies are limited to marinol, with mixed results.

4.8.8.2 INFLAMMATORY BOWEL DISEASES (CROHN'S DISEASE, ULCERATIVE COLITIS).

The endocannabinoid system and IBD

"Endocannabinoid system changes have been observed in the gastrointestinal tracts of experimental animal models of IBD, as well as in those of IBD patients [5,155]. These changes include changes in the levels of endocannabinoids, cannabinoid receptors, and endocannabinoid synthesizing and degrading enzymes."[4,5,155,156,157,158]

and

Surveys and clinical studies with cannabis:

"Findings from a cross-sectional survey of 291 patients with IBD (Crohn's disease or ulcerative colitis) suggested that the vast majority of those patients reported using cannabis to relieve abdominal pain and to improve appetite[22]. In contrast to patients with Crohn's disease, a greater proportion of patients with ulcerative colitis reported using cannabis to improve diarrheal symptoms[22]. In general, patients reported being more likely to use cannabis for symptom relief if they had a history of abdominal surgery, chronic analgesic use, alternative/complementary medicine use, and a lower SIBDQ (short inflammatory bowel disease questionnaire) score[22]. Both ulcerative colitis and Crohn's disease patients reported using cannabis to improve stress levels and sleep[22]. The mean duration of cannabis use (current or previous) was seven years. The majority of cannabis users reported using once per month or less, but 16% reported using cannabis daily or several times per day[22]. The vast majority (77%) of users reported smoking the cannabis as a joint without tobacco, 18% of users smoked it with tobacco, 3% used a water pipe, and 1% reported oral ingestion[22]. Approximately one-third of patients in this study reported significant side effects associated with the use of cannabis such as paranoia, anxiety, and palpitations. Other commonly reported side effects included feeling high, dry mouth, drowsiness, memory loss, hallucinations, and depression. [22]

A retrospective, observational study of 30 patients with Crohn's disease examined disease activity, use of medication, need for surgery, and hospitalization before and after cannabis use [41]. The average duration of disease was 11 years (range: 1 - 41 years). Twenty patients suffered from inflammation of the terminal ileum, five had inflammation of the proximal ileum, and eight had Crohn's disease of the colon. The indication for cannabis was lack of response to conventional treatment in the majority of the patients, and chronic intractable pain in most of the other patients [41]. Most patients smoked cannabis as joints (0.5 g cannabis/joint), a few inhaled the smoke through water, and one patient consumed cannabis orally [41]. Of those who smoked cannabis, most smoked between one and three joints per day. One patient smoked seven joints per day. The average duration of cannabis use was two years (range: 2 months - 9 years). All patients reported that consuming cannabis had a positive effect on their disease activity [41]. The scores on the Harvey-Bradshaw index (an index of Crohn's disease activity) were significantly decreased following cannabis use, and the use of other medications (e.g. 5-ASA, corticosteroids, thiopurine, methotrexate, and TNF antagonist) also appeared to be significantly reduced following use of cannabis [41]. The study was limited by design and small size.

A preliminary, observational, open-label, prospective, single-arm trial in a group of 13 patients suffering from Crohn's disease or ulcerative colitis reported that treatment with inhaled cannabis over a three-month period improved subjects' quality of life, caused a statistically significant increase in subjects' weight, and improved the clinical disease activity index in patients with Crohn's disease[35]. Patients reported a statistically significant improvement in their perception of their general health status, their ability to perform daily activities, and their ability to maintain a social life[35]. Patients also reported a statistically significant reduction in physical pain, as well as improvement in mental distress[35]. No serious adverse events were noted. Study limitations included study design, subject selection bias, the lack of a proper control group and placebo, small number of subjects, and the inability to establish a dose-response effect." [35]

4.8.8.3 DISEASES OF THE LIVER (HEPATITIS, FIBROSIS, STEATOSIS, ISCHEMIA-REPERFUSION INJURY, HEPATIC ENCEPHALOPATHY).

4.8.8.4 METABOLIC SYNDROME, OBESITY, DIABETES.

4.8.8.5 DISEASES OF THE PANCREAS (DIABETES, PANCREATITIS).

Note: for sections 4.8.8.3, 4.8.8.4, and 4.8.8.5 below, no clinical studies examining the role of cannabis in the treatment of these disorders have been carried out to date.

There is evidence that the endocannabinoid system has a role in these conditions but more study is required before this info becomes clinically relevant.

4.8.9 ANTI-NEOPLASTIC PROPERTIES.

"A number of studies have implicated the endocannabinoid system in the pathophysiology of cancer. In general, endocannabinoids seem to have a protective effect against carcinogenesis, and proper regulation of local endocannabinoid tone is likely an important factor in controlling the malignancy of different cancers[159]. When compared with healthy tissues, the levels of endocannabinoids appear to be elevated in glioblastomas, meningiomas, pituitary adenomas, prostate and colon carcinomas, and endometrial sarcomas[156,160,161,162,163,164]. The expression levels of cannabinoid receptors are also differentially regulated in normal versus malignant cells, with increased or decreased levels of these receptors varying with cancer type (reviewed in[159]). Such differences in the levels of endocannabinoids and in the patterns of expression levels of cannabinoid receptors across different cancer types reflect the complex role of the endocannabinoid system in cancer and are likely to pose challenges to potential therapeutic approaches. Nonetheless, a number of pre-clinical studies have shown that endocannabinoids, certain synthetic cannabinoid agonists, and some phytocannabinoids can inhibit tumour growth and progression of numerous types of cancers through various mechanisms including promotion of apoptosis, cell-cycle arrest/growth inhibition, and prevention of metastasis through inhibition of tumour invasion, migration, and neo-angiogenesis (reviewed in [159,165])."

4.8.10 EMERGING POTENTIAL THERAPEUTIC USES.

"There are a few pre-clinical reports which suggest that administration of a low dose of THC, a CB1 receptor antagonist, or a CB2 receptor agonist may reduce the progression of atherosclerosis in mouse models of the disease." [166,167,168]

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CONSUMER INFORMATION

[N]Cannabis (Marihuana, marijuana)

Cannabis (marihuana, marijuana) is not an approved therapeutic product and the provision of this information should not be interpreted as an endorsement of the use of cannabis for therapeutic purposes, or of cannabis generally, by Health Canada. Cannabis has not been authorized through the standard Health Canada drug approval process because the available scientific evidence does not establish the safety and efficacy of cannabis to the extent required by the *Food and Drug Regulations* for marketed drugs in Canada.

This leaflet is designed by Health Canada for patients authorized to possess dried marihuana for medical purposes. It is based on the document "*Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the Cannabinoids*" that can be found at http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php, and is a summary only - it will not provide you with all the facts about marihuana for medical purposes.

Contact your health care practitioner if you have any questions.

ABOUT THIS PRODUCT

What the product may be used for:

Your health care practitioner may have authorized the use of cannabis for the relief of one or more of the following symptoms associated with a variety of disorders which have not responded to conventional medical treatments. These symptoms (or conditions) may include: severe refractory nausea and vomiting associated with cancer chemotherapy; loss of appetite and body weight in cancer patients and patients with HIV/AIDS; pain and muscle spasms associated with multiple sclerosis; chronic non-cancer pain (mainly neuropathic); severe refractory cancer-associated pain; insomnia and depressed mood associated with chronic diseases (HIV/AIDS, chronic non-cancer pain); and symptoms encountered in the palliative/end-of-life care setting. This is not an exhaustive list of symptoms or conditions for which cannabis may be authorized for use by your health care practitioner.

The potential therapeutic and adverse effects associated with cannabis use may vary depending on the amount of cannabis used and the concentration of cannabinoids in the cannabis product, the frequency of cannabis use, the patient's age and medical condition, previous experience with cannabis or cannabinoids, and the use of other prescription or non-prescription drugs. For more detailed information on potential therapeutic uses and adverse effects, please consult the "*Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the Cannabinoids*".

What the active ingredients might be:
Tetrahydrocannabinol (THC)
Cannabidiol (CBD)

The type and amount of these ingredients may vary depending on the cannabis strain.

What the other ingredients might be:
There are over 70 different cannabinoids as well as hundreds of other chemicals in cannabis. Many of the chemicals found in tobacco smoke are also found in smoke from burning cannabis.

What the product does:
The principal active ingredient in cannabis (THC) acts on very specific targets found in the body known as cannabinoid receptors. Cannabinoids may also have targets other than the cannabinoid receptors. Cannabinoid receptors are found throughout the body, in most tissues and organs, but they are especially numerous in the brain and nervous system. Cannabinoid receptors are involved in the regulation of many bodily functions including: brain and nervous system activity, heart rate and blood pressure, digestion, inflammation, immune system activity, perception of pain, reproduction, wake/sleep cycle, regulation of stress and emotional state and many other functions. For more detailed information, please consult the "*Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the Cannabinoids*".

When the product should not be used:

Cannabis should not be used if you:
- are under the age of 18
- are allergic to any cannabinoid or to smoke
- have serious liver, kidney, heart or lung disease
- have a personal or family history of serious mental disorders such as schizophrenia, psychosis, depression, or bipolar disorder
- are pregnant, are planning to get pregnant, or are breast-feeding

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- are a man who wishes to start a family
- have a history of alcohol or drug abuse or substance dependence

Talk to your health care practitioner if you have any of these conditions. There may be other conditions where this product should not be used, but which are unknown due to limited scientific information.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The use of this product involves risks to health, some of which may not be known or fully understood. Studies supporting the safety and efficacy of cannabis for therapeutic purposes are limited and do not meet the standard required by the *Food and Drug Regulations* for marketed drugs in Canada.
- Smoking cannabis is not recommended. Do not smoke or vapourize cannabis in the presence of children.
- Cannabis may impair your ability to drive, operate heavy or complex machinery, or perform other activities requiring alertness or coordination for 24 hours or longer after consumption.
- Cognitive impairment may be greatly increased when cannabis is consumed along with alcohol or other drugs which affect the activity of the nervous system (e.g. opioids, sleeping pills, other psychoactive drugs)

INTERACTIONS WITH THIS PRODUCT

Cannabis may interact with several drugs. Make sure to tell your health care practitioner which prescription drugs, non-prescription drugs or herbal products you are currently taking, particularly:

- Any drugs which slow down the central nervous system, causing drowsiness. These may include sleeping pills, tranquilizers, some pain medications, some allergy or cold medications, or anti-seizure medications.
- Antiretroviral drugs used in the treatment of HIV/AIDS.
- Other drugs such as certain anti-depressants, stomach acid inhibitors, certain antibiotic and antifungal medications, certain heart medications, and Saint John's Wort.

DOSING INFORMATION AND ROUTES OF ADMINISTRATION

There is no scientifically defined dose of cannabis for any specific medical condition. If you have not consumed cannabis before, it would be prudent to have someone with you the first time you use it. Dosing remains highly individualized and relies greatly on titration (i.e. finding the right dose where potential therapeutic effects are maximized while adverse effects are minimized). However, the current available information suggests most individuals use less than 3 grams daily of dried marihuana for medical purposes, whether it is taken orally, inhaled, or a combination of both.

Patients with no prior experience with cannabis or cannabinoids are cautioned to begin at a very low dose and to stop therapy if unacceptable or undesirable effects occur.

There are only a handful of small clinical studies of short duration on the use of smoked/vapourized cannabis for therapeutic purposes. Smoking/vapourizing cannabis results in a more rapid onset of action (within minutes), higher blood levels of cannabinoids, and a shorter duration of effects compared to oral ingestion. While there are no established dosing guidelines for smoking/vapourizing cannabis for therapeutic purposes, it is prudent to proceed slowly and cautiously in a gradual fashion, waiting between puffs or inhalations for a few minutes to gauge for strength of effects or for possible overdosing. A dosing increase should be carried out slowly, only if required, and only until you reach a comfortable dose.

In contrast to smoked/vapourized cannabis, there are no clinical studies of cannabis-based edible products for therapeutic purposes. Absorption of these products by the oral route is known to be slow and erratic, and the onset of effects is delayed with the effects lasting much longer compared to smoking/vapourizing. Furthermore, dosages for orally administered products are even less well-established than for smoking/vapourization. If ingesting cannabis orally (e.g. in foods) wait between 30 and 60 minutes between bites of cannabis-based oral products to gauge for strength of effects or for possible overdosing.

Stop using cannabis right away and consult your health care practitioner if you begin to experience any side effects (see side effects section for additional information).

Please consult the "*Daily amount and dosing information fact sheet*" for additional information on dosing. The fact sheet can be found at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/daily-quotidienne-eng.php.

OVERDOSE

Symptoms of overdose may include: sleepiness, confusion, disorientation, clumsiness/loss of coordination, fainting, dizziness, chest pain, fast, slow or pounding heartbeat, panic attacks, loss of contact with reality, and seizures.

Seek immediate medical attention in case of drug overdose, and especially if experiencing chest pain, panic attacks, loss of contact with reality, or seizures.

Cannabis should be used with caution in patients receiving concomitant therapy with other psychoactive drugs because of the potential for greatly enhanced effects on the brain and other parts of the nervous system. An overdose can also occur if a patient is smoking/vapourizing cannabis and at the same time consuming orally administered cannabinoids whether from prescription cannabinoid medications, or from consumption of teas, baked goods or other products.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The information on side effects associated with therapeutic use of cannabis is limited. Some of the more well-known side effects are intoxication-like reactions including:

- dizziness, drowsiness, feeling faint or lightheaded, fatigue, headache;
- impaired memory and disturbances in attention, concentration and ability to think and make decisions;
- disorientation, confusion, feeling drunk, feeling abnormal or having abnormal thoughts, feeling "too high", feelings of unreality, feeling an extreme slowing of time;
- suspiciousness, nervousness, episodes of anxiety resembling a panic attack, paranoia (loss of contact with reality), hallucinations (seeing or hearing things that do not exist);
- impairments in motor skills and perception, altered bodily perceptions, loss of full control of bodily movements, falls;
- dry mouth, throat irritation, coughing;
- nausea, vomiting; and
- fast heartbeat.

Long term use may:

- increase the risk of triggering or aggravating psychiatric and/or mood disorders (schizophrenia, psychosis, anxiety, depression, bipolar disorder);
- increase the risk of developing respiratory infections or chronic cough (when smoking);
- decrease sperm count, concentration and motility, and increase abnormal sperm morphology;
- negatively impact the behavioural and cognitive development of children born to mothers who used cannabis during pregnancy;
- negatively affect cognitive functions (ability to think and make decisions);
- lead to a decrease in one or more of the drug's effects over time (tolerance);
- lead to withdrawal-type symptoms when use is abruptly halted or discontinued. Withdrawal symptoms may include anger or aggression, irritability, anxiety, nightmares/strange dreams, insomnia/sleep difficulties, craving, headache, restlessness, and decreased appetite or weight loss, depressed mood, chills, stomach pain, shakiness and sweating; and
- result in psychological dependence (addiction) which is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

This is not a complete list of side effects. If you experience any side effects or any unexpected effects while taking cannabis for medical purposes, stop consuming cannabis immediately and contact a health care practitioner or the emergency department of your nearest hospital.

How the product is supplied:

Dried marihuana plant material.

How to store the product

Store in a cool place, preferably away from light and air. See manufacturer's instructions on the product label for recommended storage conditions.

Keep marihuana out of the reach of children and locked in a safe place to prevent theft and misuse. This product should not be shared with anyone else.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of this product to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health care practitioner. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full information prepared for health professionals (the "*Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the Cannabinoids*") can be found on the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php

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