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MEMO

TO: Donna Bain, Chief Operating Officer (A)
FROM: P.McKenna Boot, MD, Medical Director Clinical Services
DATE: 04 July 2016
SUBJECT: Medical Marijuana Health Care Advice Document Update

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Medical marijuana refers to the physician-supported use of the marijuana plant for therapeutic purposes. Medical marijuana is not considered a drug by Health Canada; individuals require documented physician support to legally obtain it. Under current Health Canada regulations, once a medical document is obtained, individuals register with a licensed producer.

The evidence for the use of medical marijuana in the treatment of chronic noncancer pain was reviewed by the WSIB in 2008. The resulting Health Care Advice document did not support the funding of medical marijuana in chronic non-cancer pain. Since then, several more studies were published. These were discussed at the Drug Advisory Committee (DAC) on March 1st, 2016. The majority of published systematic reviews and clinical trials were not relevant to the WSIB population since they investigated non-compensable illnesses such as multiple sclerosis and HIV-associated neuropathies. Only one short-term randomized-controlled trial of smoked medical marihuana in neuropathic pain was identified as relevant; however, despite a positive result, it had major design limitations. The DAC concluded the additional evidence is insufficient to support a change in position. The DAC further recommended, in the rare circumstance when an injured worker obtains entitlement for medical marijuana, WSIB should adhere to reasonable dosing limitations due to safety issues. Additionally, approvals should be consistent with WSIB's overall approach to generic substitution.

Clinical Services supports the DAC recommendations and in response will update the Health Care Advice document. With your approval of this DAC recommendation, this information will be communicated to staff.

Approved by:

D.Bain, PhD

HEALTH CARE ADVICE

Medical Marijuana and Chronic Non-Cancer Pain

Status

The term medical marijuana in this document refers to the physician-supported use of the marijuana plant for therapeutic purposes. This document pertains specifically to the use of *medical marijuana for the treatment of chronic non-cancer pain (CNCP)* in conditions relevant to the Workplace Safety and Insurance Board (WSIB). The marijuana plant remains illegal for general consumption in Canada.

This document is not intended to act as a reference for the use of medical marijuana in the treatment of cancer pain, nor for the use of marijuana plant derivatives/synthetic cannabinoids that are sold as drug products in Canada (e.g., Sativex® and Cesamet®).

Recommendation

Medical marijuana for CNCP should not be approved for payment by the WSIB Drug Benefit Program. This recommendation is based on a review of the literature that revealed:

- The majority of published systematic reviews and clinical trials were not relevant to the WSIB population, as they investigated non-compensable illnesses such as multiple sclerosis and HIV-associated neuropathies and studied the effects of synthetic prescription cannabinoids (not medical marijuana).
- One short-term randomized controlled trial (RCT) investigating cannabis use in neuropathic pain reported a reduction in pain intensity with cannabis use over a 5 day treatment period in comparison with placebo; however, numerous study limitations were noted.
- Three other non-peer reviewed systematic reviews sponsored by Workers' Compensation Board-Alberta (2002), Alberta Heritage Foundation for Medical Research (2004), and the Evidence Based Practice Group, WorkSafe BC (2006) have similarly concluded that there is no robust evidence for the efficacy of medical marijuana in the treatment of CNCP.
- There are numerous established and potential safety concerns associated with the use of medical marijuana.
- Health Canada's *Marihuana for Medical Purposes Regulations (MMPR)* only pertain to the authorization to possess marijuana for medical purposes. Health Canada has not approved cannabis as a drug under the *Food and Drugs Act*. The licensing of producers by Health Canada does not represent an opinion by the federal ministry as to the justification for using medical marijuana to treat symptoms of a disease or illness.
- A review of other Workers' Compensation Boards positions across Canada in July 2012 revealed that none of the other Boards approve of the use of medical marijuana.
- Overall, no evidence has been published comparing cannabis with an active comparator. The published RCTs are not considered robust and have major limitations. Medical marijuana should not be approved for payment in the treatment of CNCP. The medical literature is reviewed regularly and the status of medical marijuana in the WSIB Drug Benefit Program will be reconsidered when substantive new evidence is available.

Background

Medical Marijuana for Therapeutic Use

Health Canada must issue a Notice of Compliance (NOC) for a drug before it can be introduced to the market. A NOC indicates that a drug has been assessed and has complied with the Food and Drugs Act and Regulations regarding safety, efficacy and quality. Health Canada has *not* issued a Notice of Compliance for marijuana for medical purposes.[1] Medical marijuana is not an approved therapeutic product in Canada and has no approved therapeutic indications.[2]

Health Canada's Regulations

For information regarding the current regulatory status of medical marijuana in Canada visit:

http://www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php

Review of the Literature

Literature Review

A review of the clinical efficacy and safety of medical marijuana in the treatment of chronic non-cancer pain (CNCP) included key guidelines and randomized controlled trials (RCTs) that were at least single-blind, and excluded clinical trials evaluating pain due to conditions not relevant to the WSIB (e.g. diabetic neuropathy, multiple sclerosis). A search for relevant systematic reviews and meta-analysis yielded no results.

One RCT investigated smoked cannabis use in individuals with neuropathic pain of at least 3 months in duration caused by trauma or surgery, with allodynia or hyperalgesia. Smoked cannabis was compared to placebo over a 5 day treatment period. Although pain intensity appeared to decrease with cannabis use, there were many limitations to the study, including small sample size (23 patients enrolled), short duration and lack of active comparators. A total of 248 mild and six moderate adverse events (fall, increased pain, numbness, drowsiness, and pneumonia) were reported during this short trial. The most commonly reported adverse events included headache, dry eyes, burning sensation, dizziness, numbness, and cough.[3]

Two other RCTs evaluating the efficacy of medical marijuana in peripheral neuropathy, spinal cord injury, type 1 complex regional pain syndrome or nerve injury were considered; however, the origin of pain in several of the participants was due to conditions not relevant to the WSIB (e.g. diabetic neuropathy, multiple sclerosis).[4, 5]

The College of Family Physicians of Canada's preliminary guidelines for medical marijuana for chronic pain or anxiety do not support the use of dried cannabis as a treatment for anxiety, insomnia, or pain conditions commonly seen in primary care, such as fibromyalgia or low back pain. The guidelines advise family physicians to recommend other treatments with more evidence of safety and efficacy for these conditions. Further research is needed on the effectiveness and long-term safety of medical marijuana compared to other standard treatment options.[6]

There were no clinical studies on the use of marijuana edibles or topicals for therapeutic purposes.[7]

Other Literature Reviews

In 2002, an evidence-based review of the literature on the use of medical marijuana was sponsored by the Workers' Compensation Board-Alberta.[8] The search included literature on medical marijuana up to September 2001. The authors concluded that "there is presently insufficient evidence to treat medical marijuana as a "prescribable" drug.

In 2004, a Health Technology Assessment by the Alberta Heritage Foundation for Medical Research was done on the Use of Cannabis or Cannabinoids for Chronic NonCancer Pain.[9] The search included literature on medical marijuana up to October 2003. None of the studies identified were

designed rigorously enough to be included in the review. The authors concluded that there was a dearth of evidence concerning the efficacy and effectiveness of medical marijuana and cannabinoids for the treatment of CNCP.

On June 22, 2006 the Evidence Based Practice Group at WorkSafe BC reported the results of an updated literature search conducted from 2003 to May 26, 2006.[10] The authors concluded medical marijuana and cannabinoids lacked evidence in the treatment of patients with CNCP.

Safety Concerns

There are demonstrated pulmonary, cardiovascular, immune, psychiatric, cognitive and psychomotor risks associated with the use of marijuana.[7,11] Intoxication, precipitation of anxiety or acute psychotic reactions, and orthostatic hypotension have been well-documented with the acute inhalation of marijuana smoke.[12]

Some evidence suggests a potential link between marijuana smoking and lung cancer; however, further higher quality studies are required.[7,13,14] Cannabis use is associated with shortness of breath, pharyngitis, hoarseness of the voice, and asthma exacerbations.[14] Cannabis use also leads to cough, increased sputum production and wheezing in about 20% of cannabis smokers,[14] and marijuana smoking may be a risk factor for periodontal disease, independent of tobacco use.[15]

The College of Family Physicians of Canada's preliminary guidelines have determined that the use of smoked cannabis is not appropriate for patients who are 25 years of age or younger, are pregnant, or have a strong family history of psychosis, current or past cannabis use disorder, substance abuse disorder, cardiovascular disease or respiratory disease. The guidelines also acknowledge that marijuana use, inhaled or ingested, is a risk factor for motor vehicle accidents, and recommend against driving after use.[6]

Pharmacokinetic trials have demonstrated that absorption of marijuana when consumed orally may be slow and erratic.[7]

Summary and Recommendations

This document refers to the use of medical marijuana (i.e., the use of marijuana plant for therapeutic purposes). There is insufficient evidence from the medical literature to support the use of medical marijuana in the treatment of CNCP and there remain concerns about potential harm.[16] Furthermore, several alternative medications that have received an NOC from Health Canada are available on the WSIB formularies for the treatment of CNCP. For these reasons, the authorization of medical marijuana for workers with chronic non-cancer pain is not recommended.

This review does not pertain to the use of medical marijuana in the treatment of cancer pain, conditions not relevant to the WSIB, or to the medical use of synthetic marijuana plant derivatives (e.g., Sativex®, and Cesamet®).

Further Information

For more information from Health Canada on the use of marijuana for medical purposes, please visit: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php

If you require further information on the medicinal use of marijuana, please contact a WSIB pharmacist at: (416) 344-2008.

Original date: 10 March 2009

Updated: 05 July 2016

References

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12. Kalant H. Smoked marijuana as medicine: not much future. *Clin Pharmacol Ther.* 2008;83(4):17-18.
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16. Deshpande A, Mailis-Gagnon A, Zoheiry N, et al. Efficacy and adverse effects of medical marijuana in chronic noncancer pain. Systematic review of randomized controlled trials. Can Fam Physician. 2015;61:e372–81

Title: Information About Medication - Cannabinoids (nabilone - Cesamet®, cannabis extract Sativex®)

Roles: Nurse Consultant (NC), Staff Physician (SP)

Please review Formulary Drug Listing Decisions: **Cannabinoids (Cesamet® capsules and Sativex® buccal spray)**

FORMULARY STATUS: **Nabilone (Cesamet®, generic brands) is listed on cancer formulary (19WS); Sativex® is not listed on any WSIB formularies**

REVIEW OF FUNDING REQUESTS

Brand new requests for cannabinoids will not be approved, unless claim meets exceptional use criteria. Payment for cannabinoids will continue for workers who were approved for entitlement. When a claim with cannabinoid entitlement comes up for review, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication, and that it merits continued entitlement.

Nabilone (Cesamet®)

Treatment of Neuropathic Pain: Due to availability of many first and second-line treatment options on WSIB formularies, nabilone should only be approved for the treatment of neuropathic pain if **criteria for exception** use are met.

Exceptional Use Criteria:

- at least two other treatments have failed to improve pain after an adequate trial.

Treatment of Musculoskeletal Injuries/Conditions: Cannabinoids have not been investigated in the treatment musculoskeletal injuries; thus, nabilone should not be approved for use in these indications.

Treatment of Spasticity due to Spinal Cord Injury: A pilot study with 11 participants showed that nabilone may be beneficial in reduction of spasticity in select muscle groups; however, the small sample size and trial design make any therapeutic advantage questionable. For alternatives useful in treatment of injury-related spasticity on 03WS (CNS) formulary, please see **Information About Medication-Skeletal Muscle Relaxants.**

Treatment of Fibromyalgia: Nabilone should not be approved for the treatment of fibromyalgia pain due to the lack of substantive evidence of efficacy and the availability of other fibromyalgia treatment options on WSIB formularies (acetaminophen, NSAIDs, SSRIs, SNRIs, gabapentin/pregabalin, TCAs).

Treatment of Sleep Disturbance: In one small trial assessing the effectiveness of nabilone on sleep disturbance in patients with fibromyalgia, nabilone demonstrated a possible therapeutic advantage over amitriptyline. As the exposure to the drug was only 2 weeks, the conclusion regarding the long-term safety and efficacy of nabilone for chronic sleep disturbance due to painful stimuli could not be extrapolated. Nabilone should only be considered for short-term use in workers with fibromyalgia who are unable to sleep and cannot tolerate all other formulary alternatives such as zopiclone, benzodiazepines, trazodone or TCAs. Nabilone should not be approved for the treatment of insomnia not caused by painful stimuli, as there is no evidence it is helpful.

Treatment of Anxiety (GAD): The anxiolytic properties of nabilone were studied in one small trial with 15 participants suffering from psychoneurotic anxiety, which is not injury-induced. Marginal improvement coupled with limitations in trial design indicate that nabilone in not a treatment option for GAD.

Treatment of PTSD Related Nightmares: Nabilone demonstrated a positive effect on one dream score in a small trial with 10 participants, but overall did not show a significant change. Due to trial limitations, any therapeutic advantage of nabilone is inconclusive. Guideline-supported PTSD treatment options, which have positive effect on nightmares and are available on WSIB formularies, include antidepressants +/- antipsychotics/anticonvulsants.

Delta-9-tetrahydrocannabinol 27 mg/ml and cannabidiol 25 mg/ml (Sativex®)

Treatment of Neuropathic Pain: Sativex® failed to demonstrate clinically significant reduction in pain severity in two out of three trials evaluating its effectiveness in the treatment of central neuropathic pain. In addition, due to its propensity to cause tolerance, drug dependence and abuse necessitating increased dosing, it should not be approved for this indication. Formulary alternatives for the treatment of neuropathic pain are numerous.

Treatment of Cancer Pain: Based on positive results from one trial with 177 cancer patients, Sativex® was granted conditional approval from Health Canada as an adjunctive analgesic treatment in adults with advanced cancer who experience refractory pain during the highest tolerated dose of around-the-clock strong opioid therapy. However, three subsequent studies (not fully published) failed to reach statistical significance in all primary endpoints compared to placebo. Therefore, Sativex® should not be approved for refractory cancer pain. Appropriate management of refractory cancer pain includes many options such as multiple opioid rotations, methadone and other adjuvant medications (gabapentin/pregabalin, TCAs, SNRIs) alone or in combination.

SAFETY OF CANNABINOIDS:

Delta-9–tetrahydrocannabinol (THC-active ingredient of Sativex®) has the potential to cause drug dependency and abuse.

Health Canada has issued a warning on the use of cannabinoids due to possibility of physical and psychological dependence, side effects (cognitive and memory impairment, changes in mood) and potential for pharmacodynamics drug interaction with other CNS depressant drugs.

Occupational hazard is present, as cannabinoids may impair coordination and mental alertness.

FORMULARY ALTERNATIVES

Various alternatives are currently available on the WSIB formularies for the treatment of pain. They include:

Nociceptive pain analgesics

Acetaminophen
Non-Steroidal Anti-Inflammatories (NSAIDs) (e.g., celecoxib, diclofenac, naproxen, ibuprofen, etc.)
Opioids (e.g., Tylenol 3®, codeine phosphate, 282®)

Neuropathic pain analgesics

Tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, imipramine)
Anticonvulsants (e.g., gabapentin, pregabalin)
Opioids (e.g., Tylenol 3®, codeine phosphate, 282®)
Serotonin Norepinephrine Reuptake Inhibitors (e.g. venlafaxine, duloxetine)

Cannabinoids vs. Opioids: Based on the available evidence, there is no proven advantage to the use of cannabinoids over opioids for pain. As monotherapy, one clinical trial actually showed that a weak opioid

(dihydrocodeine) was more effective and better tolerated than nabilone.

Combination treatment in Neuropathic Pain: Nabilone and Sativex® have never been investigated as add-on therapies except in multiple sclerosis and cancer pain setting, although synergistic effect in neuropathic pain is an attractive option to improve analgesic efficacy and reduce doses. Cannabinoids should be used with caution in individuals on other sedating drugs. There is a significant risk of adverse effects associated with combining cannabinoids with opioids, TCAs and anticonvulsants.

COMPARATORS

Cannabinoids as an Alternative to Medical Marijuana : There is insufficient quality evidence from the medical literature to support the use of medical marijuana in the treatment of chronic non-cancer pain (CNCP). In addition, medical marijuana is not an approved therapeutic product in Canada and the concern is potential harm, psychiatric effects, pulmonary toxicity (if smoked) and abuse. For more information see **Health Care Advice Document: Medical Marijuana.** There is paucity of available research on the use of cannabinoids as substitutes for medical marijuana. Treatment with cannabinoids should be considered in light of the available evidence of efficacy and safety of these registered drug products.

Standard Forms and Letters

NC Denied Medication (not funded) Sample Decision Letter

Policy and Operational

(17-01-02) Entitlement to Health Care
Workplace Safety and Insurance Act, 1997, as amended Part IV Health Care

References

Formulary Drug Listing Decisions: Cannabinoids (WSIB website)

Tools

List of Medication and Formulary References

formulary (19WS) and Sativex® not be listed on any WSIB formularies.

Original date: 11 May 2009

Updated: 29 January 2013

Updated: 04 July 2016