



WORKING TO MAKE A DIFFERENCE

STEERING COMMITTEE:

- Director, Research Secretariat (Policy & Research)
- Vice President, Assistant CFO & Executive Sponsor (CMS)
- Director, Long Term Disability & ODS (WES)
- Director, CMS (WES)
- Senior Client Services Manager, ODS (WES)
- CMO & Director, Clinical & Health Care Services (WES)

Evidence Based Practice Group (EBPG)

EBPG Membership

Senior
Medical
Advisor

Manager,
Medical
Services

Manager,
Policy and
Practice

Manager,
Client
Services

Pharmacy
Advisor

Statistical
Analyst –
Health Care

June 22, 2006

Re: Medical Marijuana. First update.

We have once again updated our review of the literature on the use of medical marijuana in treating patients with chronic, non malignant pain states. There is no substantive evidence to suggest that it is of benefit to such patients. Our conclusions remain valid and unchanged from 2003, namely:

- There continues to be insufficient evidence to support the concept that marijuana is a “prescribable” drug. The organization should not “approve” any such requests.
- Requests for pharmaceutical grade cannabinoid derivatives in claims accepted for multiple sclerosis and/or occupational cancers may be considered and should require input from a senior medical advisor.

Feel free to review the background documentation at:

http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp

Craig W Martin, M.D.
Chair, Evidence Based Practice Group
Senior Medical Advisor
WorkSafeBC

CWM/kt

Efficacy of marijuana in treating chronic non cancer pain

A Short Review.

By

WCB Evidence Based Practice Group
Dr. Craig W. Martin, Senior Medical Advisor

June 2006

<u>TABLE OF CONTENTS</u>	Page
Background.....	1
Objectives	1
Methods	1
Results	2
Conclusions.....	5
References.....	6
Appendix I	7

Background:

In June 2003, the Evidence Based Practice Group (EBPG) published a memo regarding Medical Marijuana based on a systematic review done by the Alberta WCB in June 2002⁽¹⁾. In this memo the EBPG concluded that:

1. there was insufficient evidence to support the concept that marijuana is a prescribable drug. WorkSafeBC should not 'approve' any such requests.
2. requests for pharmaceutical grade cannabinoid derivatives (c.q. Marinol[®]) in cancer or HIV related claims may be considered and should require input from a senior medical advisor.

Since the publication of this EBPG memo on Medical Marijuana, Health Canada have granted approval to 3 synthetic cannabinoids, including Sativex[®], Marinol[®] and Cesamet[®]. Sativex[®] has been approved by Health Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis⁽²⁾. Marinol^{®(3)} and Cesamet^{®(4)} have been approved by Health Canada for treating severe nausea and vomiting associated with cancer chemotherapy.

Objectives:

The objectives of this short systematic review are to answer following questions:

- Is cannabis or cannabinoid, natural or synthetic (including Marinol[®], Sativex[®], Cesamet[®]) effective in treating chronic non cancer pain?
- Is there any new evidence to change the WorkSafeBC policy on marijuana use in treating chronic non cancer pain?

Methods:

Through the Evidence Based Practice Group's (EBPG) regular literature surveillance, prior to the request for this review, we have seen two systematic reviews on this topic. The systematic review by Campbell et al was published in the British Medical Journal in 2001⁽⁵⁾ and a more recent one was published by the Alberta Heritage Foundation for Medical Research (AHFMR) in February 2004⁽⁶⁾. Upon examination, the systematic review by Campbell et al⁽⁵⁾ was also included in the systematic review from the AHFMR⁽⁶⁾. Hence, the EBPG has undertaken to update this systematic review by the AHFMR⁽⁶⁾.

Systematic literature searches, from 2003 to May 26, 2006, were undertaken on Ovid[®] based commercial medical literature databases including Cochrane Database of Systematic Review, American College of Physician Journal Club, Database of Abstracts of Review of Effectiveness, Cochrane Controlled Trial Registry, BIOSIS[®], CINAHL[®], EMBASE[®], The International Pharmaceutical Abstracts, MEDLINE[®] In-Process, Other Non-Indexed Citations and MEDLINE[®].

Other non commercial databases including Bandolier, the US Agency for Healthcare Research and Quality, the US Institute for Clinical System Improvement and the NHS Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (DARE) at the University of York Database; and

websites of members of the International Network of Agencies for Health Technologies Assessment (including Alberta, Ontario and the Quebec Office of Health Technology Assessment in Canada, the US, Great Britain, France, New Zealand, Australia, Sweden and Denmark) were also searched.

Searches were undertaken by employing a combination of keywords (chronic pain) AND (cannabis sativa OR cannabis OR cannabinoid OR marijuana OR marihuana OR marinol OR sativex OR cesamet OR delta-9-tetrahydrocannabinol OR cannabidiol OR dronabinol OR cannabinal OR nabilone OR delta-9-tetrahydrocannabinol-cannabidiol OR delta 9 tetrahydrocannabinol). The search was limited to human and English language literature (at least abstracts available in English). The search was not limited to any study designs. However, only evidence available from randomized/controlled trials was to be used to update the AHFMR systematic review⁽²⁾.

Results:

109 articles were identified from these searches. Of the 109 articles identified, 6 were thought to be relevant to the purpose of updating the AHFMR systematic reviews⁽⁶⁾. These 6 articles were retrieved in full⁽⁷⁻¹²⁾. Of these 6 articles, the following ones will not be discussed further due to various reasons including:

- Berlach et al⁽⁷⁾ wrote a case series on 20 adult patients with chronic non cancer pain that have been treated with nabilone and followed up for an average of 1.5 years.
- Berman et al⁽⁸⁾ reported a randomized double blind controlled trial three period cross over trial among 48 chronic non-cancer pain patients due to brachial plexus avulsion. It seems that the same research by Berman et al has been reported twice i.e. in 2003⁽¹³⁾ and 2004⁽⁸⁾. The one reported in 2003 is included in the AHFMR systematic review⁽⁶⁾.
- A double blind cross-over randomized trial among 21 patients diagnosed with chronic neuropathic pain was published in October 2003 in JAMA⁽¹⁰⁾. This article, reported by Karst et al, is included in the AHFMR systematic review⁽⁶⁾.

Hence there are 3 articles in total that will be discussed and analyzed in further detail.

The AHFMR use of cannabis or cannabinoids for non-malignant chronic pain⁽⁶⁾.

The purpose of this systematic review was to describe the background and the current evidence on the efficacy/effectiveness of cannabis or cannabinoids for the management of non-malignant chronic pain and to determine the feasibility of the use of cannabis or cannabinoids by patients in rural communities. The EBPG will summarize the evidence on the efficacy/effectiveness of cannabis or cannabinoids for the management of chronic non-malignant pain below.

The authors searched various databases from 1998 to October 2003. These databases included Cochrane Library, the UK York University CRD, The UK National Institute for Clinical Excellence (NICE), CINAHL, PubMed, Science Citation Index, Embase, AMED, TRIP, Bandolier, the US ECRI, the US National Guideline Clearinghouse, the US NLM Gateway, the US FDA, the US Medicare Coverage, Health Canada, the Canadian Newstand, the Quebec AETMIS, the Canadian Coordinating Office of Health Technology Assessment, CMA Infobase, the Alberta Medical Association Clinical Practice Guidelines Program, the Alberta Health and Wellness, Metabrowser, Cabot (grey literature database), the US Clinical trial database and the UK National Research Register. Various keywords combination were employed in these searches. These keywords included pain, chronic pain, chronic disease, marijuana, marihuana and cannabis.

Systematic reviews and RCTs published in English language from 1998 to October 2003 were included in the analysis. Patients diagnosed with non-malignant chronic pain (pain persisting for > 3 months) were included. Patients with cancer related, acute or post-operative pain were excluded. Animal studies were excluded. Any intervention with cannabis or cannabinoids (both synthetic and natural) using any route of administration, including tablets, capsules, sprays, inhalants or inhaled smoke, were included. Any medical, mechanical or surgical intervention designed to treat patients with non-malignant chronic pain, comparison between different cannabis/cannabinoid treatment regimens, placebo or no treatment comparisons were included in the analysis. Only studies which had outcomes related to changes (perceived or actual) in pain severity due to the intervention being studied were included in the analysis.

One systematic review and 4 randomized controlled trials (RCTs) met their inclusion criteria. The included systematic review (by Campbell et al⁽⁵⁾) assessed RCTs of cannabis or cannabinoids in the treatment of cancer, post-operative and chronic non-malignant pain. Although the review included the terms cannabis and cannabinoids in its search strategy, no studies were found on the use of cannabis. Two crossover studies of cannabinoids, each with only one patient who had chronic non-malignant pain, were included. Pain relief was the same for patients treated with tetra hydro cannabinol or codeine, which were both better than placebo. *It should be noted that these 2 RCTs were of 'n of 1' studies (i.e. based on trial on each individual patients) hence it would be considered very low level evidence.*

Four double blind placebo controlled trials^(8,10,14,15) (3 cross over studies) used either placebo only or placebo and other cannabinoid compounds as comparator intervention against tetra hydro cannabinol, cannabinoids or cannabis based medicinal extracts. All of these RCTs reported a significant improvement in pain symptoms for patients treated with cannabinoids compared to placebo. However, the route of administration, dosage, the type and the source of the active compound (synthetic or natural) varied between studies, so the optimum treatment regimen for cannabinoids remains unclear. The mode of action of cannabinoids in chronic pain patients was also still unclear. The effectiveness of cannabis (smoked, ingested or imbibed) in relieving chronic pain was unknown since none of the included studies assessed this method of use.

The authors concluded that, at the time, there was a paucity of evidence on the efficacy and effectiveness of cannabis or cannabinoids for the management of chronic non-malignant pain. The EBPG considered this systematic review as good quality level 1 evidence (Appendix 1). *It should be noted that the EBPG does not have access to some of the databases employed in this systematic review.*

Critical analysis of the three studies from the EBPG systematic search subsequent to the AHFMR report⁽⁶⁾.

Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies⁽¹¹⁾.

Notcutt presented the results of 34 patients mainly with chronic neuropathic pain in a 'n of 1' trial design. The patients were treated with 3 cannabis based medicinal extracts (delta 9 tetrahydrocannabinol, cannabidiol and a 1:1 mixture of both) given over a 12 week period. After an initial open-label period, the cannabis based medicinal extracts were used in a randomized, double-blind, placebo controlled, crossover trial. The authors found that extracts which contained delta 9 tetrahydrocannabinol proved most effective in symptom control. The authors mentioned that side-effects were common and related to the dosing experiments. *The EBPG does not accept the n of 1 study design as one of acceptable evidence in conducting systematic review in assessing the efficacy/effectiveness of certain treatment modalities. The EBPG considers n of 1 trial design as a hypothesis generating study design. Hence, this study by Notcutt et al⁽¹¹⁾ will not be reviewed further.*

Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis⁽¹²⁾.

Rog et al conducted a single-center, 5-week (1-week run-in, 4-week treatment), randomized, double-blind, placebo-controlled, parallel-group trial in 66 patients with multiple sclerosis and central pain states of a whole plant cannabis based medicinal extract containing delta 9 tetrahydrocannabinol and cannabidiol delivered via an oromucosal spray, as adjunctive analgesic treatment. Each spray delivered 2.7 mg of tetrahydrocannabinol and 2.5 mg of cannabidiol. Patients can gradually self-titrate to a maximum of 48 sprays in 24 hours.

Sixty-four patients (97%) completed the trial, 34 of whom received cannabis based medicinal extract. Pain and sleep disturbance were recorded daily on an 11-point numerical rating scale. The authors found that cannabis based medicinal extract was superior to placebo in reducing the mean intensity of pain (mean change -2.7, 95% CI: -3.4 to -2.0 compared to placebo -1.4 95% CI: -2.0 to -0.8, $p = 0.005$) and sleep disturbance (cannabis based medicinal extract mean change -2.5, 95% CI: -3.4 to -1.7 compared to placebo -0.8, 95% CI: -1.5 to -0.1, $p = 0.003$). The authors concluded that cannabis based medicinal extract was effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain

The EBPG considers the study by Rog et al⁽¹²⁾ to be good quality level 1 evidence. ***However, it should be noted that the study was conducted among multiple sclerosis patients. The difference in pain reduction between patients treated with cannabis based medicinal extract was very small (0.7 on 11 point scale) and the authors did not provide long enough follow up data.***

Long term effects of exposure to cannabis⁽⁹⁾.

In this paper, Iversen assessed the long term effects of exposure to cannabis. *This paper is not a systematic review on the side effects of cannabis. The authors did not provide explanations on the method of how primary studies used in this report were gathered.* However, several points that may be of importance included that that long-term use of cannabis, particularly at high intake levels, was associated with several adverse psychosocial features, including lower educational achievement and, in some instances, psychiatric illness. There was little evidence, however, that long-term cannabis use causes permanent cognitive impairment, nor was there any clear cause and effect relationship to explain the psychosocial associations. There were some potential physical health risks noted, particularly the possibility of damage to the airways in cannabis smokers.

Conclusions:

At present, there is no evidence on the effectiveness of cannabis or cannabinoids in treating patients with chronic non-malignant pain. Given the current availability of evidence on the effectiveness of cannabis or cannabinoids on treating chronic non-malignant pain, the EBPG suggests that the WorkSafeBC policy on the 'medicinal use' of cannabis or cannabinoids in treating chronic pain, as outlined in the 2002 paper entitled 'Marijuana for medicinal purposes: an evidence based assessment'⁽¹⁾ remains appropriate and should not be modified.

References:

1. Fisher B, Johnston D, Leake P. (June 2002). Marijuana for medicinal purposes: an evidence based assessment. A research project sponsored by Medical Services. Workers' Compensation Board – Alberta. Downloaded from http://www.worksafebc.com/health_care_providers/Assets/PDF/marijuana_medicinal_purposes.pdf in May 30, 2006.
2. .. Sativex[®] Complete Drug Monograph. Downloaded from <http://e-cps.pharmacists.ca/CPHA/main.htm> in June 12, 2006.
3. .. Marinol[®]. Complete Drug Monograph. Downloaded from <http://e-cps.pharmacists.ca/CPHA/main.htm> in June 12, 2006.
4. .. Cesamet[®] Complete Drug Monograph. Downloaded from <http://e-cps.pharmacists.ca/CPHA/main.htm> in June 12, 2006.
5. Campbell FA, Tramer MR, Carroll D et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ*. 2001;323(7303):13-16.
6. ..Technote. Use of cannabis or cannabinoids for non-malignant chronic pain (February 2004). Alberta Heritage Foundation for Medical Research. Health Technology Assessment. Downloaded from <http://www.ahfmr.ab.ca/download.php/6d3b1f36e8bad158824ab55612fa6b5a> . in March 2004.
7. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Medicine*. 2006;7(1):25-29.
8. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of randomized controlled trial. *Pain*. Dec 2004;112(3):299-306.
9. Iversen L. Long term effects of exposure to cannabis. *Current Opinion in Pharmacology*. 2005;5(1):69-72.
10. Karst M, Salim K, Burstein S et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain. A randomized controlled trial. *JAMA*. Oct 2003;290(13):1757-1762.
11. Notcutt W, Price M, Miller R et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia*. May 2004;59(5):440-452.
12. Rog DJ, Nurmikko TJ, Friede T and Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65(6):812-819.
13. Berman J, Lee J, Cooper M et al. Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of randomized controlled trial. *Anaesthesia*. 2003;58(9):938.
14. Wade DT, Robson P, House H et al. A preliminary controlled study to determine whether whole plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical Rehabilitation*. 2003;17(1):21-29.
15. Zajicek J, Fox K. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo controlled trial. *Lancet* 2003;362(9395):1517-1526.

Appendix 1. Workers' Compensation Board of BC - Evidence-based Practice group. Grades of quality of evidence (adapted from 1,2,3,4).

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic reviews of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Reference.

1. Canadian Task Force on the Periodic Health Examination: The periodic health examination. CMAJ. 1979;121:1193-1254.
2. Houston TP, Elster AB, Davis RM et al. The US Preventive Services Task Force Guide to Clinical Preventive Services, Second Edition. AMA Council on Scientific Affairs. American Journal of Preventive Medicine. May 1998;14(4):374-376.
3. Scottish Intercollegiate Guidelines Network (2001). SIGN 50: a guideline developers' handbook. SIGN. Edinburgh.
4. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ. Aug 5, 2003;169(3):207-208