Evidence-Based Practice Group Answers to Clinical Questions

Cannabis / Wound Healing / Infections

A Rapid Systematic Review

By

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WORK SAFE BC
WORKING TO MAKE A DIFFERENCE

Clinical Services – Worker and Employer Services

About this report

Cannabis / Wound Healing / Infections

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

To determine whether there is an association between cannabis use and wound healing, or susceptibility to infections.

Background

In Canada, cannabis became legally available on October 17, 2018. In 2018, 9.5% of the Canadians aged 15 or older reported non-medical and 2.8% medical cannabis use in the previous year. [1] In the period of 1985-2015, overall cannabis use increased and subsequent to 2004 the increase was profound in adults aged 25 and over. [2] In 2017, British Columbia produced the highest amount of the Canadian grown cannabis (36.6%), and had the second highest cannabis consumption per capita following Nova Scotia (24.6 grams and 27.1 grams per person per year, respectively). [3]

The chemical compounds in cannabis are known as cannabinoids and are purported to be responsible for the health effects. Besides these plant derived cannabinoids (e.g., Cannabis sativa or Cannabis indica species), there are other exogenous cannabinoids, such as the synthetic nabilone and nabiximols. Also, there are endogenous cannabinoids (endocannabinoids) as produced "on demand" from cellular phospholipid precursors in human body. [4] One major cannabinoid component in cannabis is Δ-9-tetrahydrocannabinol (THC) with known psychoactive effects, whereas another important one, cannabidiol (CBD), is known to be non-psychoactive. There are over 60 cannabinoids [5] and their physiologic effects may vary. Where THC's effects on immune systems (e.g., cytokines, splenocytes, antibodies, and on chemotaxis) are widely recognized [6] CBD is also shown to have anti-inflammatory and antinociceptive properties. [7]

The human immune system uses various functional mechanisms; such as barriers, complement system, T and B lymphocytes, phagocytes, monocytes, neutrophils, eosinophils, macrophages, natural killer cells, and responds to hormones, neurotransmitters, proteins and lipids (e.g., endocannabinoids). Some immune system cells contain cannabinoid membrane receptors (CB1 and CB2) and respond to both endocannabinoids and exogenous cannabinoids, such as marijuana or synthetic compounds. [5] CB1 receptors are primarily located in the Central Nervous System (CNS); but also exist in peripheral tissues (e.g., adrenal glands, thymus, tonsils, lungs, heart, bone marrow). CB2 receptors are more commonly expressed in peripheral immune tissues (e.g., spleen, thymus, blood cells –neutrophils, monocytes, natural killer cells, and B lymphocytes–), but can also exist in the CNS. [5, 8] Both CB1 and CB2 cannabinoid receptors are found throughout the skin. Any

clinical effects of cannabis would depend on whether it is signaled via the CB1 or CB2 receptors. [9]

The effect of cannabinoids on the immune system is a complex one. They may play a role in increasing or suppressing activities of selected immune cells, in stimulating or inhibiting immunologic mechanisms; and/or they may lead to anti- or pro-inflammatory responses. [4] Whether some deficits potentially triggered by cannabinoids lead to greater susceptibility to infections (especially for immunocompromised patients), or to an overly increased immunity that leads to increased allergic responses or autoimmune diseases, or to acceptable protective immune effects needs to be determined by future, high quality research studies. [10] The Health Canada report 'Information for Health Care Professionals - Cannabis (marihuana, marijuana) and the Cannabinoids', which is available online includes a section titled 'Immune system' (page 156) where the complex nature of the immunophysiologic effects of cannabinoids are explained in detail. [4]

To date, the majority of the studies exploring the effects of cannabis/cannabinoids on immune systems were experimental animal studies and in vitro cell-culture studies. [6, 11, 12] A few clinical studies explored markers for neuroimmune function in human subjects. [13, 14] Some researchers suggested that cannabis use may stimulate appetite in HIV infected patients [4, 15] and others studied the effect of cannabinoids on HIV viral load. [16] In terms of immune competence or susceptibility to infectious diseases, a number of clinical studies either with cannabis or synthetic cannabinoids have indicated an increased number of infections (e.g., urinary and respiratory tract infections) in treatment groups compared to controls. [17-19] A review by Tahamtan specifically focused on the effects of the cannabinoids and cannabinoid receptors on viral infections and called for caution when using pharmaceutical cannabinoids for patients with viral infections. [20] Another review by Eisenstein focused on the effects of cannabinoids on T-cells and on resistance to infection. [21] A hypothesis generating review by Lehman et al. highlighted the role of the endocannabinoid system in CNS-injury induced immunodeficiency syndrome (CIDS). They stated that the CB2 receptor activation following a head injury initiated immunosuppression might be useful in the early (pro-inflammatory) stages after an injury. They also suggested this same phenomenon may later lead to CIDS with its inherent increased risk of infections (e.g., pneumonia and urinary tract infections). [22]

The literature on cannabis and wound healing includes studies on wound pain [23, 24] and on the role of the endocannabinoid system in wound healing, mostly focusing on CB2 receptor function. [25-29] A 2016 mice study found that CB2 receptor activation enhanced keratinocyte proliferation and migration, decreased fibroblast accumulation and transformation, as well as collagen I

expression, suggesting a reduction in inflammation, enhancement of epithelization and decreased scar formation, hence improved wound healing. [30] Another study by Yang et al. using mouse corneal epithelial cells found that CB1 receptor activation boosted wound healing and decreased fibrosis, hence could potentially help with corneal wound healing by suppressing the innate immune responses after injury. [31] One experimental wound healing study, an in vitro model with human colonic epithelial cells, found that CB1 receptors were generally expressed in the apical zone of normal colonic epithelium, and that there was increased epithelial expression of CB2 receptors during the acute phase of inflammatory bowel disease. [28] One other study with rat and human cells found that the endocannabinoid system played an important role in periodontal wound healing. The authors observed that the endocannabinoid system helped in "healing granulation tissue, enhancing the fibroblast proliferation and cell repopulation for wound filling". [32] However, at present, clinical research do not support use of cannabinoids for topical dermatologic treatment. Efficacy and safety data for available products are limited, product formulations are not standardized and regulation is poor. [33] Also, application of topical cannabinoids on active healing areas of the wound may lead to contamination and infection. [4]

Methods

To determine whether there is an association between cannabis consumption, especially cannabis smoking and infection susceptibility or wound healing, a systematic literature search was conducted on February 6, 2019.

OvidSP Search:

- The following commercial medical databases were utilized: Cochrane Central Register of Controlled Trials December 2018; Cochrane Database of Systematic Reviews 2005 to January 30, 2019; Health Technology Assessment 4th Quarter 2016, Embase 1974 to 2019 February 5; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 5, 2019 which were available through the OvidSP platform.
- The search was conducted by employing different keywords combined using appropriate Boolean Operators (AND /OR).

  marijuana OR cannabis OR cannabinoid OR cannabidiol OR delta-9 tetrahydrocannabinol OR tetrahydrocannabinol OR endocannabinoid OR THC OR CBD

  AND

  Wound healing OR infection susceptibility

- The search captured 275 citations.
- Duplicates were removed and 198 citations were left.
- When limited to 'humans', 'adults' and 'adolescents' (13 to 18 years), 'English language', and 'last 10 years' 95 citations remained.

Results

OvidSP Search

- Out of the 95 citations, 21 citations [7, 9, 22-25, 31, 32, 34-46] were selected
- Four [34, 38, 45, 46] of the 21 citations were conference abstracts and were excluded:
    - Endocannabinoids and growth factors cross-talk in the process of wound healing (Cardinali, 2014) [34]
    - Simultaneous activation of C-X-C chemokine receptor 4 and cannabinoid receptor 2 results in decreased angiogenesis (Scarlett, 2015) [46]
    - Cannabinoid receptor 1 (CB1R) activation induces alveolar macrophages to acquire a proinflammatory and profibrotic phenotype in pulmonary fibrosis (Park, 2017) [38]
    - Cannabidiol (CBD) oil use in epidermolysis bullosa (Zinn, 2017) [45]
- Abstracts were collected for the remaining 17 citations
- After the abstracts were reviewed, full-text articles were collected for three [9, 32, 35]
    - **Self-initiated use of topical cannabidiol oil for epidermolysis bullosa** (Chelliah, 2018) → A 3-case series report on the use of topical cannabidiol (CBD) for congenital blistering dermatoses (observational study based on self-report, with no controls). The cases were 6-month, 3-year and 10-year old. The authors reported reduced pain and blistering, as well as rapid wound healing after topical CBD oil/cream application. (Level of evidence 4. Appendix 1)
    - **The risks and benefits of cannabis in the dermatology clinic** (Dhadwal, 2018) → This was a narrative review on cannabis use in dermatologic settings. The authors listed the dermatologic indications for medical marijuana that were accepted by selected states in the USA. These included severe pain, lupus, nail-patella syndrome, neurofibromatosis, psoriasis. However, the authors reported that except for the use of cannabis products for pain (e.g., for hidradenitis suppurativa), the literature supporting other indications was very weak. As per the prospective medical use of cannabis in dermatology clinics they listed potential indications such as acne, eczematous eruptions, cholestatic pruritus, skin cancer, systemic sclerosis and wound healing. With regards to wound healing the authors referred to a single study by Wang et al. (2016). [30] This study, using a mouse model, reported that activating CB2 receptors might potentially help wound healing with decreasing

inflammation and fibrosis, and increasing epithelization. The study also referred to the necessity of a certain amount of inflammation and collagen deposition for wound healing and for maintaining skin's mechanical property. The authors of the narrative review, Dhadwal et al., noted some dermatologic risks associated with cannabis use; such as cannabis smoking related oral cancers, oral stomatitis and candidiasis; as well as cannabis arteritis which presents with occlusion of the peripheral arteries (digital necrosis, ulcers, venous thrombosis) and cannabis allergy (e.g., mild urticarial reactions, angioedema). The authors called upon dermatologists to be cautious because of these possible adverse effects from cannabis use. (Level of evidence 5. Appendix 1)

- **Involvement of the endocannabinoid system in periodontal healing** (Kozono, 2010) → The authors conducted a study with both rat and human cells to explore the role of the endocannabinoid system in periodontal wound healing. They explored CB1 and CB2 receptor expressions in rat gingival connective tissue using an experimental wound model. They observed that cannabinoids helped proliferation of gingival fibroblasts via CB1 and CB2 receptors, and cannabinoid receptor expression was upregulated in the granulation tissue during periodontal healing. They concluded that endocannabinoid system was important for "healing granulation tissue, enhancing the fibroblast proliferation and cell repopulation for wound filling". (Level of evidence 4. Appendix 1)

Additional Search:

- We found two additional articles [5, 47] via hand searching the references of the selected articles and through a quick PubMed search
  - **Immunoregulatory Role of Cannabinoids during Infectious Disease** (Hernández-Cervantes, 2017) → This narrative review by Hernández-Cervantes et al. is a comprehensive one, which incorporated currently available research evidence. The authors first detailed how the immune and endocannabinoid systems worked. They then reviewed the role of the endocannabinoid system in bacterial, viral, parasitic and fungal infections separately. They had tabulations for the studies in each category, also listing the type of the cannabinoid used and the effects observed. The findings were mixed and differed by infectious agent category (bacteria, virus, parasites, and fungus). There were differences across in vivo, in vitro and clinical studies within each infectious agent category. The

authors stated that "the immune system is responsible for eliminating pathogens and the cannabinoid receptors are present in the immune cells", hence it was important to continue with studies exploring the role of cannabinoids within the immune function. (Level of evidence 5. Appendix 1)

- **Dermatological aspects of synthetic cannabinoid addiction** (Inci, 2017) → This was a cross-sectional study performed in clinical settings, in a Research, Treatment and Training Center for Alcohol and Substance Dependence. The study included 136 patients (enrolled between Sep 2014 and Sep 2015) who were synthetic cannabinoid addicts according to the DSM-4 classification. The authors collected data by patient interviews, examination, and medical tests when required. They found that the patients mostly complained about periorbital darkening, hallowed-cheeks and premature aging, hair loss, gray hair, and acnes. The findings from dermatologic examinations were classified into six groups (skin, hair and hairy scalp, nail, oral mucosa, nasal mucosa findings, and genital findings). The most common findings were artifact lesions (e.g., blade scars, tobacco scars-stains), tattoos, and acne. The authors referred to the ever-evolving street drug market and invited dermatologists to be aware of signs of synthetic cannabinoid use which may help "facilitate earlier diagnose, intervention, and directed treatment." (Level of evidence 4. Appendix 1)

Summary

- There is a scarcity of clinical studies on the topic (i.e., the association between cannabis and infection susceptibility, or wound healing)
- Existing clinical studies demonstrate major limitations including those of;
    - study design (case studies, case series, cross-sectional studies…)
    - small sample sizes
    - insufficient data collection to study adverse effects
    - limited number of immunologic markers used (narrow scope)
    - unclear/insufficient information on cannabis/cannabinoid exposure (duration, intervals, amount of the substance used)
    - unaddressed potential confounders (e.g., cigarette smoke, alcohol use)
- Most studies concerned with the health effects of cannabis/ cannabinoids recognize the interaction between cannabinoids and immune systems
- To explore the effects of cannabinoids on the immune system commonly in vitro human and in vivo/in vitro animal experimental study designs are employed
- When different infectious agents (bacteria, virus, parasites, and fungus) are present, modulation of the immune system by cannabinoids vary
- While studies with bacteria are inconclusive (in vitro and in vivo tests showing opposite results); in general it is suggested that during virus infections cannabinoids modulate immune system negatively, and during parasite infections, positively
- The studies exploring the effects of cannabis/cannabinoids on infectious agents in human subjects and susceptibility for infections are scarce (mostly, on HIV positive patients)
- To better assess the effects of cannabis use on susceptibility to infections, long-term studies that assess variation or cessation in cannabis use (not only at baseline), possibly over intervals, is needed

- Regarding the effect of cannabinoids on wound healing, there are findings from animal studies indicating inflammation reduction and re-epithelialization enhancement; hence improved wound healing

- Human studies on cannabinoids and wound healing are insufficient (e.g., limited efficacy and safety data, no standardized formulations, and poor regulation) for currently available topical cannabis products; hence, risk for contamination and infection

- Both the effect of cannabinoids on infection susceptibility and on wound healing require better quality clinical studies

- Legalization of cannabis use in Canada may enable Canadian researchers to conduct more research studies (e.g., potentially, less regulatory barriers, larger study samples, chance to compare different quantity/quality/type of cannabis products)

Conclusion

The current literature on the association between cannabis use and wound healing or susceptibility to infections is mixed and inconclusive.

References

1. Statistics Canada. *National Cannabis Survey, third quarter 2018*. 2018 cited 2019; Available from: https://www150.statcan.gc.ca/n1/en/daily-quotidien/181011/dq181011b-eng.pdf?st=G5Nc3Z_S.
2. Rotermann, M. and R. Macdonald, *Analysis of trends in the prevalence of cannabis use in Canada, 1985 to 2015.* Health Rep, 2018. 29(2): p. 10-20.
3. Statistics Canada. *Provincial and Territorial Cannabis Economic Accounts, 2017*. The Daily 2018 April 30, 2018; Available from: https://www150.statcan.gc.ca/n1/en/daily-quotidien/180430/dq180430b-eng.pdf?st=rVvaQdQz.
4. Health Canada. *Information for Health care Professionals - Cannabis (marihuana, marijuana) and the cannabinoids* 2018 cited 2019; Available from: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf.
5. Hernandez-Cervantes, R., et al., *Immunoregulatory Role of Cannabinoids during Infectious Disease.* Neuroimmunomodulation, 2017. 24(4-5): p. 183-199.
6. Blumstein, G.W., et al., *Effect of Delta-9-tetrahydrocannabinol on mouse resistance to systemic Candida albicans infection.* PLoS One, 2014. 9(7): p. e103288.
7. Styrczewska, M., et al., *Flax Fiber Hydrophobic Extract Inhibits Human Skin Cells Inflammation and Causes Remodeling of Extracellular Matrix and Wound Closure Activation.* BioMed Research International, 2015. 2015 (no pagination)(862391).
8. Atwood, B.K. and K. Mackie, *CB2: a cannabinoid receptor with an identity crisis.* Br J Pharmacol, 2010. 160(3): p. 467-79.
9. Dhadwal, G. and M.G. Kirchhof, *The risks and benefits of cannabis in the dermatology clinic.* Journal of Cutaneous Medicine and Surgery, 2018. 22(2): p. 194-199.
10. National Academies of Sciences, E., and Medicine. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. 2017 cited 2019; Available from: https://www.ncbi.nlm.nih.gov/books/NBK423845/pdf/Bookshelf_NBK423845.pdf.
11. Cabral, G.A., J.C. Lockmuller, and E.M. Mishkin, *Delta 9-tetrahydrocannabinol decreases alpha/beta interferon response to herpes simplex virus type 2 in the B6C3F1 mouse.* Proc Soc Exp Biol Med, 1986. 181(2): p. 305-11.
12. Buchweitz, J.P., et al., *Modulation of airway responses to influenza A/PR/8/34 by Delta9-tetrahydrocannabinol in C57BL/6 mice.* J Pharmacol Exp Ther, 2007. 323(2): p. 675-83.
13. Bredt, B.M., et al., *Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients.* J Clin Pharmacol, 2002. 42(S1): p. 82S-89S.
14. Thames, A.D., et al., *Combined effects of HIV and marijuana use on neurocognitive functioning and immune status.* AIDS Care, 2016. 28(5): p. 628-32.
15. Whiting, P.F., et al., *Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.* JAMA, 2015. 313(24): p. 2456-73.
16. Abrams, D.I., et al., *Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial.* Ann Intern Med, 2003. 139(4): p. 258-66.
17. Zajicek, J.P., et al., *Multiple sclerosis and extract of cannabis: results of the MUSEC trial.* J Neurol Neurosurg Psychiatry, 2012. 83(11): p. 1125-32.
18. Devinsky, O., et al., *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.* N Engl J Med, 2017. 376(21): p. 2011-2020.
19. Ware, M.A., et al., *Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS).* J Pain, 2015. 16(12): p. 1233-1242.

20. Tahamtan, A., et al., *Effects of cannabinoids and their receptors on viral infections.* J Med Virol, 2016. 88(1): p. 1-12.
21. Eisenstein, T.K. and J.J. Meissler, *Effects of Cannabinoids on T-cell Function and Resistance to Infection.* J Neuroimmune Pharmacol, 2015. 10(2): p. 204-16.
22. Lehmann, C., et al., *Inhibition of the cannabinoid 2 receptor in CNS-injury induced immunodeficiency syndrome.* Medical Hypotheses, 2014. 82(6): p. 736-739.
23. Maida, V. and J. Corban, *Topical Medical Cannabis: A New Treatment for Wound Pain-Three Cases of Pyoderma Gangrenosum.* Journal of Pain and Symptom Management, 2017. 54(5): p. 732-736.
24. Mervis, J.S. and D.G. Federman, *Pain Management in Patients with Chronic Wounds.* Current Dermatology Reports, 2018. 7(3): p. 136-146.
25. Ruhl, T., B.S. Kim, and J.P. Beier, *Cannabidiol restores differentiation capacity of LPS exposed adipose tissue mesenchymal stromal cells.* Experimental Cell Research, 2018. 370(2): p. 653-662.
26. Du, Y., et al., *Cannabinoid 2 receptor attenuates inflammation during skin wound healing by inhibiting M1 macrophages rather than activating M2 macrophages.* Journal of Inflammation (United Kingdom), 2018. 15 (1) (no pagination)(25).
27. Li, S.S., et al., *Cannabinoid CB2 receptors are involved in the regulation of fibrogenesis during skin wound repair in mice.* Molecular Medicine Reports, 2016. 13(4): p. 3441-3450.
28. Wright, K., et al., *Differential expression of cannabinoid receptors in the human colon: Cannabinoids promote epithelial wound healing.* Gastroenterology, 2005. 129(2): p. 437-453.
29. Zheng, J.L., et al., *Cannabinoid receptor type 2 is time-dependently expressed during skin wound healing in mice.* International journal of legal medicine, 2012. 126(5): p. 807-814.
30. Wang, L.-L., et al., *Pharmacological activation of cannabinoid 2 receptor attenuates inflammation, fibrogenesis, and promotes re-epithelialization during skin wound healing.* European Journal of Pharmacology, 2016. 786: p. 128-136.
31. Yang, Y., et al., *Cannabinoid receptor 1 suppresses transient receptor potential vanilloid 1-induced inflammatory responses to corneal injury.* Cellular Signalling, 2013. 25(2): p. 501-511.
32. Kozono, S., et al., *Involvement of the endocannabinoid system in periodontal healing.* Biochemical and Biophysical Research Communications, 2010. 394(4): p. 928-933.
33. Hashim, P.W., et al., *Topical cannabinoids in dermatology.* Cutis, 2017. 100(1): p. 50-52.
34. Cardinali, G., et al., *Endocannabinoids and growth factors cross-talk in the process of wound healing.* Journal of Investigative Dermatology, 2014. 2): p. S64.
35. Chelliah, M.P., et al., *Self-initiated use of topical cannabidiol oil for epidermolysis bullosa.* Pediatric Dermatology, 2018. 35(4): p. e224-e227.
36. Heck, D.E., et al., *Increased expression of the endocannabinoid system in mouse skin following exposure to sulfur mustard and nitrogen mustard (mechlorethamine).* FASEB Journal. Conference: Experimental Biology, 2016. 30(Meeting Abstracts).
37. Izzo, A.A. and M. Camilleri, *Cannabinoids in intestinal inflammation and cancer.* Pharmacological Research, 2009. 60(2): p. 117-125.
38. Park, J.K., et al., *Cannabinoid receptor 1 (CB1R) activation induces alveolar macrophages to acquire a proinflammatory and profibrotic phenotype in pulmonary fibrosis.* American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 2017. 195(no pagination).
39. Ramot, Y., et al., *A novel control of human keratin expression: Cannabinoid receptor 1-mediated signaling down-regulates the expression of keratins K6 and K16 in human keratinocytes in vitro and in situ.* PeerJ, 2013. 2013 (1) (no pagination)(e40).

40. Robinson, E., E. Murphy, and A. Friedman, *Knowledge, Attitudes, and Perceptions of Cannabinoids in the Dermatology Community.* Journal of drugs in dermatology : JDD, 2018. 17(12): p. 1273-1278.
41. Robledo, S.M., et al., *Studies in vitro and in vivo of antileishmanial activity and differential cytotoxicity of cannabis spp.* Planta Medica International Open. Conference: 65th Annual Meeting of the Society for Medicinal Plant and Natural Product Research, GA, 2017. 4(Supplement 1).
42. Schmuhl, E., et al., *Increase of mesenchymal stem cell migration by cannabidiol via activation of p42/44 MAPK.* Biochemical Pharmacology, 2014. 87(3): p. 489-501.
43. Solinas, M., et al., *Cannabidiol inhibits angiogenesis by multiple mechanisms.* British Journal of Pharmacology, 2012. 167(6): p. 1218-1231.
44. Yang, H., et al., *Epidermal growth factor receptor transactivation by the cannabinoid receptor (CB1) and transient receptor potential vanilloid 1 (TRPV1) induces differential responses in corneal epithelial cells.* Experimental Eye Research, 2010. 91(3): p. 462-471.
45. Zinn, Z., et al., *Cannabidiol (CBD) oil use in epidermolysis bullosa.* Pediatric Dermatology, 2017. 34 (Supplement 1): p. S17.
46. Scarlett, K.A., et al., *Simultaneous activation of C-X-C chemokine receptor 4 and cannabinoid receptor 2 results in decreased angiogenesis.* Cancer Research. Conference: 106th Annual Meeting of the American Association for Cancer Research, AACR, 2015. 75(15 SUPPL. 1).
47. Inci, R., et al., *Dermatological aspects of synthetic cannabinoid addiction.* Cutan Ocul Toxicol, 2017. 36(2): p. 125-131.

Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence

(adapted from 1,2,3,4)

1	Evidence from at least one properly randomized controlled trial (RCT) or systematic review 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 one 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.

References

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.