ARE CANNABINOIDS AND OPIOIDS NEEDED?

The Changing Landscape of Chronic Pain Management.

**Learning Objectives:**

1. **Be aware of the 2017 Canadian guideline for opioids in chronic non-cancer pain**
2. **Understand the potential role of cannabis in chronic pain management**
3. **Become familiar with tools to monitor chronic pain**

**Disclosures**

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<tr>
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RESEARCH ARTICLE

Pain in IBD Patients: Very Frequent and Frequently Insufficiently Taken into Account

Jonas Zeitl1, *, Melker Al1, Séverine Müller-Motief2, Sylvie Schae11, Luc Biedermann1, Nicolas Fourrier1, Pascal Frei1, Valerie Ritter1, Michael Seبار11, Michael Fried1, Gerhard Rögler111, Stephan Vavricka1,*, Swiss IBD Cohort Study Group1

1 Division of Gastroenterology and Hepatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland, 2 Division of Pulmonology, Zurich Rehabilitation Center Wald, Wald, Switzerland, 3 Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland, 4 Gastroenterology Bethanien, Zurich, Switzerland, 5 Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland, 6 Division of Gastroenterology, Triemli Spital, Zurich, Switzerland

* These authors contributed equally to this work.
† Membership of the Swiss IBD Cohort Study (sIBDCS) is provided in the Acknowledgments.
* jonas.zeitl@usz.ch

Abstract

Background
Pain is a common symptom related to inflammatory bowel disease (IBD). In addition to abdominal pain, pain can also be an extraintestinal manifestation of IBD. Pain treatment is challenging and a substantial part of IBD patients are treated with opioids. Therefore, a better knowledge on pain symptoms is crucial for a better therapeutic approach to this clinical problem.

Methods
Patients of the Swiss IBD Cohort Study (sIBDCS) (n = 2152) received a questionnaire regarding pain intensity, pain localization and impact of pain on daily life and social activities. Furthermore, the questionnaire investigated the use of pain-specific medication.
Systematic review: interventions for abdominal pain management in inflammatory bowel disease

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¹Florence Nightingale Faculty of Nursing & Midwifery, King’s College London, London, UK
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Email: christine.norton@kcl.ac.uk

Funding information
None.

Summary

Background: Abdominal pain is frequently reported by people with inflammatory bowel disease (IBD), including in remission. Pain is an under-treated symptom.

Aim: To systematically review evidence on interventions (excluding disease-modifying interventions) for abdominal pain management in IBD.

Methods: Databases (MEDLINE, EMBASE, PsycInfo, CINAHL, Scopus, Cochrane Library) were searched (February 2016). Two researchers independently screened references and extracted data.

Results: Fifteen papers were included: 13 intervention studies and two cross-sectional surveys. A variety of psychological, dietary and pharmacological interventions were reported. Four of six studies reported pain reduction with psychological intervention including individualised and group-based relaxation, disease anxiety-related Cognitive Behavioural Therapy and stress management. Both psychologist-


Pain - An unpleasant sensory and emotional experience associated with real or perceived tissue damage

~IAFP Definition
Ontario urged to act quickly on opioid crisis

Tory MPP calls on government to devote 10 per cent of its ad budget to warning of opioid drug dangers.

Oct 04, 2017 by Rob Ferguson

Health Minister Eric Hoskins said the government has been working on getting education materials geared toward “an effective message reaching those at risk.” - Andrew Francis Wallace / Toronto Star
Neuroinflammation—a co-occurring phenomenon linking chronic pain and opioid dependence
Catherine M Cahill\textsuperscript{1,2} and Anna MW Taylor\textsuperscript{3}

Chronic pain is a disease that encompasses both sensory and emotional elements. Opioids are highly effective analgesics because they target both of these elements, by inhibiting pain pathways and alleviating negative affect (including depression) by engaging reward or hedonic pathways. Unfortunately, chronic opioid use is limited by the development of unwanted side effects, such as tolerance, hyperalgesia, and abuse liability. Thus, the challenge of providing effective pain treatment while minimizing these unwanted side effects is an ongoing issue with significant clinical and societal impact. In this review, we posit that neuroinflammation within the central nervous system is a shared phenomenon between chronic pain and opioids that contributes to pain sensitization and negative affect. The implications for pain progression, addiction liability, and alternative treatment strategies are discussed.

Addresses
\textsuperscript{1} Department of Anesthesiology and Perioperative Care, University of California, Irvine 837 Health Sciences Road, Irvine, CA 92695, USA
\textsuperscript{2} Department of Biomedical and Molecular Sciences, Queen’s University, 5117 Botannal Hall, Kingston, Ontario K7L 3N6, Canada
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prescriptions dedicated to long-term opioid therapy. However, the conundrum of providing effective pain treatment while minimising prescription opioid abuse has become a major challenge. There are alarming statistics on therapeutic opioid misuse, although the abuse of therapeutic opioids is largely a result of diversion (obtaining opioids from family and friends) [2]. In the United States in 2013, over 37% of all drug overdose deaths could be attributed to prescription opioids. The United States Center for Disease Control and Prevention (CDC) reported, for the first time, that drugs surpassed the leading cause of death in 16 states over car accidents. However, not everyone exposed to opioid analgesics becomes addicted to their medication. The question that needs to be addressed is what makes patients susceptible to opioid misuse. We will argue that a commonality of chronic pain and opioid misuse is dysphoria and the occurrence of neuroinflammation. This immune response contributes to dysphoria and drives negative affect by disrupting mesocorticolimbic dopaminergic circuitry responsible for reward and motivation. Dampered reward circuitry is a causative factor in many psychiatric illnesses including depression, and neuroinflammation also exacer-
Cannabis use amongst patients with inflammatory bowel disease
Simon Lai\textsuperscript{a,b}, Neeraj Prasad\textsuperscript{b}, Manijeh Ryan\textsuperscript{a}, Sabrena Tangri\textsuperscript{a}, Mark S. Silverberg\textsuperscript{b}, Allan Gordon\textsuperscript{a} and Hillary Steinhart\textsuperscript{a}

\textbf{Background} Experimental evidence suggests the endogenous cannabinoid system may protect against colonic inflammation, leading to the possibility that activation of this system may have a therapeutic role in inflammatory bowel disease (IBD). Medicinal use of cannabis for chronic pain and other symptoms has been reported in a number of medical conditions. We aimed to evaluate cannabis use in patients with IBD.

\textbf{Methods} One hundred patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD) attending a tertiary-care outpatient clinic completed a questionnaire regarding current and previous cannabis use, socioeconomic factors, disease history and medication use, including complimentary alternative medicines. Quality of life was assessed using the short-inflammmatory bowel disease questionnaire.

\textbf{Results} A comparable proportion of UC and CD patients reported lifetime (48/95 (51\%) UC vs. 91/189 (48\%) CD) or current (11/95 (12\%) UC vs. 30/189 (16\%) CD) cannabis use. Of lifetime users, 14/43 (33\%) UC and 40/80 (50\%) CD patients have used it to relieve IBD-related symptoms, including abdominal pain, diarrhea and reduced appetite. Patients were more likely to use cannabis for symptom relief if they had a history of abdominal surgery (29/48 (60\%) vs. 24/74 (32\%); \textit{P}=0.002), chronic analgesic use (29/41 (71\%) vs. 25/81 (31\%); \textit{P}<0.001), complimentary alternative medicine use [36/86 (55\%) vs. 18/56 (32\%); \textit{P}=0.01] and a lower short inflammatory bowel disease questionnaire score (48.1 \pm 2.1 vs. 56.3 \pm 1.5; \textit{P}=0.03). Patients who had used cannabis [60/139 (43\%) were more likely than nonusers [13/133 (10\%); \textit{P}<0.001 vs. users] to express an interest in participating in a hypothetical therapeutic trial of cannabis for IBD.

\textbf{Conclusion} Cannabis use is common amongst patients with IBD for symptom relief, particularly amongst those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index. The therapeutic benefits of cannabinoid derivatives in IBD may warrant further exploration. 

\textit{Eur J Gastroenterol Hepatol} 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

\textbf{European Journal of Gastroenterology & Hepatology} 2011, 00:000–000

Keywords: cannabis, complimentary alternative medicine, Crohn's disease, inflammatory bowel diseases, ulcerative colitis

\*The IBD Clinic, Mount Sinai Hospital, Toronto, Ontario, Canada and \*Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Salford, UK

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Tel.: +44 161 208 5148; fax: +44 161 208 4600; e-mail: simon.lai@sft.nhs.uk

Received 15 March 2011 Accepted 6 June 2011
Fig. 1

Frequency of cannabis use by patients. Patients who used cannabis for inflammatory bowel disease symptom relief used it more frequently than those who did not use it for symptom relief.
Fig. 2

Percentage of patients using cannabis for symptom relief according to current and/or previous therapies.
The Endocannabinoid System: Receptors and Ligands

I. Receptors
- 7-member transmembrane G-protein-coupled receptor
  - CB1
  - CB2

II. Endogenous Ligands
- Anandamide (AEA)
- 2-Arachidonoylglycerol

- Synthesized from membrane-derived phospholipids
- Taken up and degraded rapidly
- Act as retrograde messengers

CB=cannabinoid.

“Relax, Eat, Sleep, Forget and Protect”
CANNABIS SATIVA
Δ⁹-TETRAHYDROCANNABINOL (THC)

- Principal psychoactive compound
- Partial agonist at CB₁ and CB₂
- Low receptor efficacy and affinity
- 11-OH-Δ⁹-THC main metabolite (more psychoactive than parent)
- Medicinal effects
  - Analgesic
  - Anti-inflammatory
  - Antiemetic
  - Antispasmodic
  - Sedative
CANNABIDIOL (CBD)

- Very low affinity for CB₁ and CB₂ and antagonist to CB₁ and inverse agonist to CB₂
- Minimal psychoactive effect
- 5-HT₁A receptor agonist
  - Antidepressant, Anxiolysis
- Allosteric modulator of mu- and delta-opioid receptors
  - Analgesia [+acts independently at CB₁ and CB₂]
- Other: Anti-psychotic, anti-epileptic
PHARMACOLOGY OF CANNABINOIDs

<table>
<thead>
<tr>
<th>Action</th>
<th>Inhaled (Smoked, Vaporized)</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Minutes with peak effect within 15 min</td>
<td>30-60 min with peak effect 2-4 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>2-4 hours</td>
<td>6-8 hours</td>
</tr>
</tbody>
</table>

- **Hepatic metabolism producing:**
  - **Principally** 11-OH-Δ⁹THC [active]
- **Elimination half life 25-36h, longer in chronic users**
- **Elimination via bile/feces (~65%) and urine (~15-30%)**
Efficacy and adverse effects of medical marijuana for chronic noncancer pain

Systematic review of randomized controlled trials

Amol Deshpande MD MBA, Angela Mailis-Gagnon MSc MD FRCPC, Nivan Zoheiry MD PhD, Shehnaz Fatima Lakha

Abstract
Objective To determine if medical marijuana provides pain relief for patients with chronic noncancer pain (CNCP) and to determine the therapeutic dose, adverse effects, and specific indications.
QUALITATIVE ASSESSMENT

Known knowns

Known unknowns

Unknown unknowns
QUALITATIVE ASSESSMENT

KNOWN KNOWNS
QUALITATIVE ASSESSMENT

KNOWN | UNKNOWNS
QUALITATIVE ASSESSMENT

UNKNOWN UNKNOWNS
Cannabis Induces a Clinical Response in Patients With Crohn’s Disease: A Prospective Placebo-Controlled Study

TIMNY NAFFAL,1 LIHI BAR-LEV SCHLEIDER,2 IRIS DOTAN,3 EPHRAIM PHILIP LANSKY,3 FABIANA SKLEPOVSKY BENJAMINOV,4 and FRED MERI KONIKOFF5

1Department of Gastroenterology and Hepatology, Meir Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Kfar Saba, 2Tishreen Center for Promotion of Medical Cannabis, Tel Aviv; 3R&D Center, Department of Gastroenterology, Sackler Medical Center, Tel Aviv; and 4Laboratory of Applied Metabolomics and Pharmacognosy, Institute of Evolution, University of Haifa, Haifa, Israel

BACKGROUND & AIMS: The marijuana plant Cannabis sativa has been reported to produce beneficial effects for patients with inflammatory bowel disease, but this has not been investigated in controlled trials. We performed a prospective trial to determine whether cannabis can induce remission in patients with Crohn’s disease.

METHODS: We studied 21 patients (mean age, 40 ± 14 yr; 13 men) with Crohn’s Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor-α agents. Patients were assigned randomly to groups given cannabis, twice daily, in the form of cigarettes containing 115 mg of Δ9-tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and 2 weeks thereafter.

RESULTS: Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; P = .43). A clinical response (decrease in CDAI score of ⩾100) was observed in 10 of 11 subjects in the cannabis group (90%; from 338 ± 185 to 152 ± 100) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; P = .028). Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.

CONCLUSIONS: Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich cannabis produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn’s disease, compared with placebo, without side effects. Further studies, with larger patient groups and a nonsmoking mode of intake, are warranted. ClinicalTrials.gov, NCT019040918.

Keywords: Inflammatory Bowel Disease; Crohn’s Disease; Cannabinoids; Endocannabinoids; Inflammation.
ADVERSE EFFECTS

Original Reports

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

Mark A. Ware, *† Tongtong Wang, ‡ Stan Shapiro, ‡‡ and Jean-Paul Collet ‡ for the COMPASS STUDY TEAM

Table 4. Unadjusted and Adjusted Rate Ratios of AEs for Medical Cannabis

<table>
<thead>
<tr>
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<th>Unadjusted IRR (95% CI)</th>
<th>Adjusted IRR* (95% CI)</th>
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<tr>
<td>All patients</td>
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<tr>
<td>Number of patients</td>
<td>215</td>
<td>216</td>
</tr>
<tr>
<td>Cumulative person-years</td>
<td>176.9</td>
<td>204.1</td>
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<tr>
<td>Number of SAEs</td>
<td>40</td>
<td>56</td>
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<tr>
<td>Number of AEs</td>
<td>818</td>
<td>574</td>
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<tr>
<td>Patients excluding &quot;current cannabis users&quot;* at baseline</td>
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<tr>
<td>Number of patients</td>
<td>74</td>
<td>216</td>
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<tr>
<td>Cumulative person-years</td>
<td>52.2</td>
<td>204.1</td>
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<tr>
<td>Number of SAEs</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>316</td>
<td>574</td>
</tr>
</tbody>
</table>

*Adjusted for age at enrollment, gender, baseline pain intensity, baseline concomitant pain medication (yes/no), disability status (yes/no), tobacco use (current vs former or never smokers), alcohol use (current vs former or never users), past cannabis use (ever/never), and study sites.

†"Current cannabis users" were those who reported using cannabis and were still using at the baseline interview.

Source: Ware 2015

- Median daily cannabis dose 2.5g/d @12.5% THC
- No increased risk of SAEs
- Most common non-serious AEs related to nervous system, gastrointestinal and respiratory [headache, nausea, nasopharyngitis, somnolence and dizziness]
PREScribing PEARLS

- NOT APPROPRIATE FOR PATIENTS WHO:
  - A) ARE UNDER THE AGE OF 25 (LEVEL II)
  - B) HAVE A PERSONAL HISTORY OR STRONG FAMILY HISTORY OF PSYCHOSIS (LEVEL II)
  - C) ARE PREGNANT, PLANNING TO BECOME PREGNANT, OR BREASTFEEDING (LEVEL II)

- AUTHORIZE WITH CAUTION IN THOSE PATIENTS WHO:
  - A) HAVE A CONCURRENT ACTIVE MOOD OR ANXIETY DISORDER (LEVEL II)
  - B) SMOKE TOBACCO (LEVEL II)
Outcomes

NRS
Brief Pain Inventory

- Amol Deshpande

2017
- Amol Deshpande

2017
- 04 [Toronto Rehabilitation Institute]
THANK YOU
Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

For related information, please see Health Canada's Information for Health Care Practitioners

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, even in particular R 6 of the ACMPR.

Your health care practitioner may use this form to provide you authorization to use cannabis for medical purposes. Your health care practitioner may use a different form, but the required information in this section 1 of the ACMPR outlined below must be included.

Access via Health Canada licensed producers: Should you choose to access cannabis from a licensed producer, this form must be signed directly by the licensed producer of your choice. You may choose any licensed producer who is authorized to sell to registered clients. Please see the Health Canada website for a list of licensed producers. Should you wish to switch from one Health Canada licensed producer to another a new medical document will be required as licensed producers are required to keep the original medical document on file.

Access via producers for own medical purposes: Should you choose to produce your own cannabis, or designate another to produce it for you, the original of this document must be sent to Health Canada with your Registration Application Form.

<table>
<thead>
<tr>
<th>Daily quantity of dried marijuana to be used by the patient</th>
<th>Drug name</th>
<th>Date of birth (DD/MM/YYYY)</th>
<th>Patient's given name and surname</th>
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<tbody>
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<td>Pounds / day</td>
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<td></td>
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<tr>
<td>The period of use is: [ ] days, [ ] weeks, [ ] months</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Note: The period of use cannot exceed one year</td>
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Health care practitioner's given name and surname

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Put business address of the location at which the patient consulted the health care practitioner (if different than above)

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<th>Fax Number (if applicable)</th>
<th>Email Address (if applicable)</th>
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</table>

Health Care Practitioner's License number

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: ____________________________

Date signed (DD/MM/YYYY): ____________

Important Note for Authorizing Health Care Practitioner

If the patient chooses to produce cannabis for their own medical purposes or you are not submitting this document via secure fax, do not initial the box below.

If your patient chooses to access cannabis for medical purposes via a licensed producer, this medical document can be submitted from the health care practitioner's office to the licensed producer by secure fax. If you choose to submit the medical document by secure fax, initial the statement below in acknowledgment agreement.

I, the health care practitioner, acknowledge that the signed medical document is the original medical document and that I have retained a copy of this document for my records only.

Initial here: ________

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations