Cannabis for inflammatory bowel disease

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**Inflammatory Bowel Diseases (IBD)**

- Chronic intestinal inflammation
- Unknown etiology
- Immune-mediated, Genetic and environmental factors
  - Chronic, recurrent exacerbations
  - Abdominal pain and diarrhea
  - Extra-intestinal symptoms (skin, joints, liver, bile ducts)
Ulcerative Colitis (UC):
Large bowel (Colon)
Superficial inflammation

Crohn’s Disease (CD):
The entire intestinal tract
Transmural inflammation
Response to Tx

- INCOMPLETE – 50-60% REMISSION RATE
- >30% NEED SURGICAL THERAPY
- NO CURE

IBD – complementary/alternative medicine

- HOMEOPATHY (55%)
- PROBIOTICS (43%)
- NATUROPATHY (43%)
- ACUPUNCTURE (33%)
- HERBAL MEDICINE (36%)

- 16-50% use marijuana

GI symptoms relieved by Cannabis

- ANOREXIA
- EMESIS
- ABDOMINAL PAIN
- DIARRHEA
- INTESTINAL INFLAMMATION

Izzo AA, Camilleri M. Gut 2008; 57: 1140
CB1 & CB2 are widely distributed in the GI tract:

- **Myenteric neurons:** Decrease intestinal hypermotility
- **Submucosal neurons:** Decrease intestinal hypersecretion
- **Immune cells:** Decrease inflammatory mediators
- **Epithelial cells:** Enhance permeability

Sharkey KA, Wiley JW. Gastroenterol 2016, 151:252
Cannabidiol in DNBS colitis

ICR mice

Control

DNBS

DNBS = Dinitrobenzene sulfonic acid

DNBS + CBD

Cannabis in human IBD

PubMed search in 2009:

N=0
Cannabis in human IBD

An observational study:

- Licensed users of medical cannabis (Tikun Olam database)
- 30 Crohn’s Disease patients
- Patients were interviewed
- Clinically relevant data

Naftali T.....Konikoff FM, IMAJ 2011, 13:455
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36</td>
<td>21–65</td>
</tr>
<tr>
<td>Male/Female</td>
<td>26/4</td>
<td></td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>11.3</td>
<td>1–41</td>
</tr>
<tr>
<td>Disease phenotype</td>
<td></td>
<td>15 luminal, 10 fistulizing, 5 fibrostenotic</td>
</tr>
<tr>
<td>Duration of cannabis consumption</td>
<td>2.1 yrs</td>
<td>3 mos–9 yrs</td>
</tr>
<tr>
<td>Amount consumed (“joints”/day)</td>
<td>2.4</td>
<td>0.5–7</td>
</tr>
</tbody>
</table>

Joint = cigarette
Clinical activity index (HBI) before and after cannabis use

- Clinical improvement in 21/30 (70%)
- HBI reduced from 14±6 to 7±6 (p<0.005)

Naftali T.....Konikoff FM, IMAJ 2011, 13:455
Medical Rx before and after cannabis use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>5-ASA</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>TNF antagonist</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

5-ASA = 5-aminosalicylic acid

Steroid sparing effect

Naftali T.....Konikoff FM, IMAJ 2011, 13:455
Conclusions

First human data of Cannabis in Crohn’s Disease:

- Beneficial clinical effects

However...

- Retrospective
- Select population

Naftali T.....Konikoff FM, IMAJ 2011, 13:455
A prospective, double-blind placebo-controlled study

ClinicalTrials.gov: NCT01040910

PATIENTS WITH MODERATE/SEVERE ACTIVE CD CANNABIS VS PLACEBO

- THC-rich cannabis Vs THC-extracted (placebo)
- 2 Cigarettes of Cannabis (=230mg THC)/day
- 8 weeks + 2 weeks “wash out”

Monitoring: CDAI, QOL, side effects, liver and kidney function
## Demographic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (N = 11)</th>
<th>Placebo group (N = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46 ± 17</td>
<td>37 ± 11</td>
<td>.02</td>
</tr>
<tr>
<td>Male</td>
<td>6 (54%)</td>
<td>6 (60%)</td>
<td>.57</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td>5 (45%)</td>
<td>5 (50%)</td>
<td>1</td>
</tr>
<tr>
<td>Current tobacco smoking</td>
<td>2 (18%)</td>
<td>3 (30%)</td>
<td>.65</td>
</tr>
<tr>
<td>Time since diagnosis of Crohn’s disease, y</td>
<td>18 ± 14</td>
<td>15 ± 8</td>
<td>.797</td>
</tr>
<tr>
<td>Involved segment of intestine&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal ileum</td>
<td>8 (72%)</td>
<td>5 (50%)</td>
<td>.38</td>
</tr>
<tr>
<td>Colon</td>
<td>4 (36%)</td>
<td>4 (40%)</td>
<td>.6</td>
</tr>
<tr>
<td>Other part of small intestine</td>
<td>3 (27%)</td>
<td>2 (20%)</td>
<td>1</td>
</tr>
<tr>
<td>Disease phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal</td>
<td>36% (4)</td>
<td>60% (6)</td>
<td>.39</td>
</tr>
<tr>
<td>Fistulizing</td>
<td>45% (5)</td>
<td>20% (2)</td>
<td>.36</td>
</tr>
<tr>
<td>Stricture</td>
<td>18% (2)</td>
<td>20% (2)</td>
<td>1</td>
</tr>
<tr>
<td>Past surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection of terminal ileum</td>
<td>45% (5)</td>
<td>60% (6)</td>
<td>.66</td>
</tr>
<tr>
<td>Partial colectomy</td>
<td>9% (1)</td>
<td>10% (1)</td>
<td>.7</td>
</tr>
<tr>
<td>Adhesioliy</td>
<td>9% (1)</td>
<td>0% (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE. Mean ± standard deviation, n (%) shown.

<sup>a</sup>One patient might have had involvement of more than 1 segment.
Effect of cannabis on CDAI

Naftali T, ...Konikoff FM. Clin GE Hepatol 2013, 11:1276
Major clinical benefits (at 8w)

Remission (CDAI<150)

- Cannabis: 50
- Placebo: 10

Off steroids

- Cannabis: 3
- Placebo: 0

Naftali T, …Konikoff FM. Clin GE Hepatol 2013, 11:1276
Quality of life

SF-36

Cannabis vs Placebo

* P<0.05

Naftali T, ... Konikoff FM. Clin GE Hepatol 2013, 11:1276
## Side-effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo Median (min-max)</th>
<th>Cannabis Median (min-max)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative side effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness *</td>
<td>4 (3-4)</td>
<td>3 (1-6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea *</td>
<td>4 (3-4)</td>
<td>4 (1-4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Concentration *</td>
<td>4 (4-5)</td>
<td>4 (4-7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Memory loss *</td>
<td>4 (4-4)</td>
<td>4 (4-6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Confusion *</td>
<td>2 (2-2)</td>
<td>2 (1-2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness *</td>
<td>2 (1-2)</td>
<td>2 (1-2)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Positive side effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain #</td>
<td>4 (3-4)</td>
<td>1 (1-2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Appetite #</td>
<td>4 (4-4)</td>
<td>2 (1-4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Satisfaction #</td>
<td>7 (3-7)</td>
<td>1 (1-4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*On a scale from 1 to 7, where 1= no effect 7=very strong effect
#On a scale from 1 to 7, where 1=very satisfied, 7= very dissatisfied
8 week course of THC-rich cannabis:

- Clinical benefit in active CD
- Steroid sparing effect
- No adverse effects

Naftali T, …Konikoff FM. Clin GE Hepatol 2013, 11:1276
1 - Cannabis in Ulcerative Colitis?

ClinicalTrials.gov: NCT01040910

- Patients with moderate/severe UC
- THC-rich Cannabis Vs Placebo
- 8 weeks treatment
- Clinical F-U + Colonoscopy
**Effect on disease activity**

**Preliminary data – 24 pts**

**Clinical**

- **Before**
  - Cannabis: 12
  - Placebo: 0

- **After**
  - Cannabis: 8
  - Placebo: 2

**Colonoscopic**

- **Before**
  - Cannabis: 2.5
  - Placebo: 1

- **After**
  - Cannabis: 2
  - Placebo: 1.5

Naftali T, ... Konikoff FM. Unpublished
Colonoscopy

Ulcerative Colitis – Before and after 8 weeks of Cannabis

June 2016  August 2016
Caution
Small study
Preliminary results
Interim analysis
final results may be different
2 - Effect of Cannabidiol?

- Patients with moderate/severe CD
- Oral CBD (10mg bid) Vs Placebo
- 8 weeks treatment
- Clinical and laboratory F-U

ClinicalTrials.gov: NCT01037322
<table>
<thead>
<tr>
<th></th>
<th>CBD</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Age (range)</td>
<td>45 (18-75)</td>
<td>32 (20-50)</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/4</td>
<td>5/4</td>
<td>NS</td>
</tr>
<tr>
<td>IBD in family</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (range)</td>
<td>10 (1-32)</td>
<td>13 (5-22)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease extent</td>
<td>TI=8 colon=2</td>
<td>TI=6 colon=4</td>
<td>NS</td>
</tr>
<tr>
<td>Past surgery</td>
<td>3</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>
Disease activity

CDAI

CBD  Placebo

P- NS

Naftali T, ... Konikoff FM. Unpublished
Clinical effects - 8w

Remission (CDAI<150)

CBD: 3/10
Placebo: 3/10

Rescue therapy

CBD: 3/10
Placebo: 3/10

Naftali T, ... Konikoff FM. Unpublished
## Side effects

<table>
<thead>
<tr>
<th></th>
<th>CBD</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1.2</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>3.8</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.8</td>
<td>3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.7</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Scale: 1-7
Conclusions

8 week course of Cannabidiol in active Crohn’s Disease:

- Safe
- But, No effect on disease activity
  - Low dose?
  - Oral route?
  - CBD not effective?
  - Synergism with other cannabis constituents?
3 - Combined CBD/THC?

ClinicalTrials.gov: NCT01826188

- Patients with moderate/severe CD
- CBD/THC 200mg/60mg (4:1) Cannabis oil Vs Placebo
- 8 weeks treatment
- Clinical + Endoscopic F-U
Disease activity

Interim analysis – 24 pts

Before

After

Clinical

Endoscopy

CDAI

CDES

CBD/THC

Placebo

CBD/THC

Placebo

Naftali T, ...Konikoff FM. Unpublished
Anti-inflammatory response

CRP

![Bar chart showing CRP levels for CBD/THC and Placebo groups at T=0 and 8w.](chart.png)

- CBD/THC: Lower CRP levels at 8w compared to T=0
- Placebo: Higher CRP levels at 8w compared to T=0

Naftali T, ... Konikoff FM Unpublished
4 – Long term safety?

- Extract safety data from Registered cannabis users (Meir Data base)

- Effect of long term (>2mos) use on patients function and wellbeing

- Monitor effect on disease activity
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>(%,range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>86/42</td>
<td>(67/33)</td>
</tr>
<tr>
<td>Age</td>
<td>39.6</td>
<td>(18-75)</td>
</tr>
<tr>
<td>Age when started</td>
<td>36.5 ±13</td>
<td>(17-72)</td>
</tr>
<tr>
<td>Crohn’s disease/UC</td>
<td>107/20</td>
<td>(84/16)</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>80</td>
<td>(63%)</td>
</tr>
<tr>
<td>IBD in family</td>
<td>37</td>
<td>(33%)</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>10 Years</td>
<td>(1-46)</td>
</tr>
</tbody>
</table>
### Duration and dose

<table>
<thead>
<tr>
<th>Duration</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration used (months)</td>
<td>38.5±21.5</td>
</tr>
<tr>
<td>Dose when started (gr/month)</td>
<td>28±16</td>
</tr>
<tr>
<td>Current dose (gr/month)</td>
<td>31±15</td>
</tr>
<tr>
<td>THC/CBD dose (gr/month)</td>
<td>0.64 ±1.1gr</td>
</tr>
</tbody>
</table>
Mode of consumption

- Smoking: 81%
- Oil: 10%
- Vaporizing: 8%
- Cookies: 1%

Naftali T, Bar Lev Schleider L...Konikoff FM. Unpublished
Effect on disease activity

Before | After >2mos

**Crohn’s Disease**

- Before: 14
- After >2mos: 6

**Ulcerative colitis**

- Before: 14
- After >2mos: 4

N=82, N=18

Naftali T, Bar Lev Schleider L...Konikoff FM. Unpublished
IBD medication use

P<0.001

Naftali T, Bar Lev Schleider L...Konikoff FM. Unpublished
Adverse effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritated eyes</td>
<td>13</td>
<td>80</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Memory decline</td>
<td>33</td>
<td>79</td>
</tr>
<tr>
<td>Confusion</td>
<td>10</td>
<td>103</td>
</tr>
<tr>
<td>Restlessness</td>
<td>8</td>
<td>104</td>
</tr>
</tbody>
</table>

Naftali T, ...Konikoff FM. Unpublished
"Positive" effects

Naftali T, Bar Lev Schleider L... Konikoff FM. Unpublished
### Adverse effects – assessed by close relative

28 relatives: 
(19 spouses, 5 parents, 4 other)

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of damage to the patient</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Signs of social problems</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Prefer the patient to stop cannabis</td>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>
Employment status

<table>
<thead>
<tr>
<th>Employment Status</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full time job</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>Part-time job</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>I did not work</td>
<td>34</td>
<td>29</td>
</tr>
</tbody>
</table>

Naftali T, ...Konikoff FM. Unpublished
Cannabis use is common in IBD
- Seems to be safe
- Preliminary clinical data support a beneficial role of cannabinoids in IBD
- Anti-inflammatory? Central? Other?
- Additional, controlled data needed!
The only RCT of cannabinoids in IBD
The road to medicalization of cannabis

- More controlled trials
- Identification of effective cannabinoid(s)
- Optimization of dosage
- Mode of delivery (Inhalation? Oral?)
- Careful monitoring of (side) effects
Thanks

Meir Med Ctr
- PROF. FRED KONIKOFF
- DR JONATHAN HIRSCH
- DR NAVE FEIRSTEIN
- DR AMIR MARI

Tikun Olam
- Lihi Bar Lev Schleider
- Dr Ephraim Lansky

Hebrew Univ
- Prof Raphael Mechoulam