Cannabis for inflammatory bowel disease

Dr Timna Naftali
Meir Hospital
Kefar Saba, Israel
Sackler School of Medicine,
Tel Aviv University,
Israel
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

complementary/alternative medicine (CAM)

- USED BY 30%–50% OF PATIENTS WITH IBD
- LESS THAN HALF REVEAL USE OF CAMS TO THEIR PHYSICIAN
- REASON:
  - side effects of standard medications
  - failure of prior therapies

Medical cannabis randomized controlled trials (RCT)

- **79 TRIALS (6462 PARTICIPANTS)**
- **IMPROVEMENT OF:**
  - chronic pain and spasticity
  - nausea and vomiting due to chemotherapy,
  - weight gain in HIV,
  - sleep disorders,
  - Tourette syndrome
- **IBD NOT AMONG INDICATIONS**

Cannabis use among IBD patients

- 67% EVER USED CANNABIS (60% IN NON IBD)
- 15-20% CURRENTLY USE OF CANNABIS
- RELIEVE ABDOMINAL PAIN, DIARRHOEA AND REDUCED APPETITE

Lal S et al, Eur J Gastroenterol Hepatol 2011; 23: 891–896
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

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 et al, 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>15 luminal, 10 fistulizing, 5 fibrostenotic</td>
<td></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 ($p<0.005$)
### 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 et al, 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

*supplied by “Tikun Olam”
## 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>Dis duration</td>
<td>18±14</td>
<td>15±8</td>
<td>.79</td>
</tr>
<tr>
<td>smoking</td>
<td>2 (18%)</td>
<td>3 (30%)</td>
<td>.65</td>
</tr>
<tr>
<td>Family history</td>
<td>5 (45%)</td>
<td>5 (50%)</td>
<td>1</td>
</tr>
</tbody>
</table>
Effect of cannabis on CDAI

Treatment:

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

Remission (CDAI<150)

<table>
<thead>
<tr>
<th></th>
<th>Cannabis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Off steroids

<table>
<thead>
<tr>
<th></th>
<th>Cannabis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3/11</td>
<td>0/10</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

SF-36

* P<0.05

T=0

8w

Cannabis

Placebo

Naftali T, ... Konikoff FM. Clin GE Hepatol 2013, 11:1276
<table>
<thead>
<tr>
<th>Side-effects</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
1 - Cannabis in Ulcerative Colitis?

ClinicalTrials.gov: NCT01040910

- Patients with moderate/severe UC
- THC-rich Cannabis* Vs Placebo
- 8 weeks treatment
- Clinical F-U

*supplied by “Tikun Olam”
Effect on disease activity

Preliminary data – 27 pts

DAI

Before

After

Quality of life

Cannabis

Placebo

Naftali T, et al Unpublished
Colonoscopy one patient

Ulcerative Colitis – Before and after 8 weeks of Cannabis

June 2016     August 2016
2 - Effect of Cannabidiol?

Patients with moderate/severe CD

Oral CBD (10mg bid)* Vs Placebo

*courtesy prof. Mechulam

8 weeks treatment

Clinical and laboratory F-U

ClinicalTrials.gov: NCT01037322

### Demographic data

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

CDAI

CBD

Placebo

T=0

8w

P- NS

Clinical effects - 8w

Remission (CDAI<150)

<table>
<thead>
<tr>
<th></th>
<th>CBD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>3/10</td>
<td></td>
</tr>
</tbody>
</table>

Rescue therapy

<table>
<thead>
<tr>
<th></th>
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<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>3/10</td>
<td></td>
</tr>
</tbody>
</table>
## 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
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

*supplied by “Tikun Olam”
Disease activity

Interim analysis – 24 pts

Before

After

Clinical

Endoscopy

CDAI

CBD/THC

Placebo

CDES

CBD/THC

Placebo

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

CRP

CBD/THC  Placebo

T=0  8w

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
## Patients

<table>
<thead>
<tr>
<th></th>
<th>No (%)(,)range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td>127</td>
</tr>
<tr>
<td><strong>Male/female</strong></td>
<td>86/42 (67/33)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>39.6 ((18-75))</td>
</tr>
<tr>
<td><strong>Age when started</strong></td>
<td>36.5 (\pm13) ((17-72))</td>
</tr>
<tr>
<td><strong>Crohn’s disease/UC</strong></td>
<td>107/20 (84/16)</td>
</tr>
<tr>
<td><strong>No comorbidity</strong></td>
<td>80 (63%)</td>
</tr>
<tr>
<td><strong>IBD in family</strong></td>
<td>37 (33%)</td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
<td>10 Years ((1-46))</td>
</tr>
</tbody>
</table>
## Duration and dose

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration used</strong> (months)</td>
<td>38.5±21.5</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>2-126</td>
</tr>
<tr>
<td><strong>Dose when started</strong> (gr/month)</td>
<td>28±16</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>5-100</td>
</tr>
<tr>
<td><strong>Current dose</strong> (gr/month)</td>
<td>31±15</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>0-80</td>
</tr>
<tr>
<td><strong>THC/CBD dose</strong> (gr/month)</td>
<td>0.64 ±1.1gr</td>
</tr>
<tr>
<td></td>
<td>5.1 ±2.9</td>
</tr>
</tbody>
</table>

Naftali T, Bar Lev Schleider L...Konikoff FM. Unpublished
Mode of consumption

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

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

Crohn’s Disease
N=82

Before
After >2mos

Ulcerative colitis
N=18

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

Before

5 ASA: 65
Steroids: 58
Immunosup: 68
Biologics: 54

After

5 ASA: 23
Steroids: 12
Immunosup: 35
Biologics: 32

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>34</td>
<td>62</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
Employment status

- Full time job: 51 Before, 64 After
- Part-time job: 14 Before, 18 After
- I did not work: 34 Before, 29 After

Naftali T, ...Konikoff FM. Unpublished
Conclusions

- 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!
Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn’s Disease, a Randomized Controlled Trial

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
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- DR AMIR MARII

Tikun Olam
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- Dr Ephraim Lansky

Hebrew Univ
- Prof Raphael Mechoulam

http://www.000x.p.com