Complementary and Alternative Medicine in IBD

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Disclosures in the past 2 yrs:

- Advisory Boards for Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada
- Consulted to Mylan Pharmaceuticals
- Educational grants from Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada
- Research grants/contracts from Abbvie, Abbvie Canada, Janssen, Celgene, Boerhinger Ingelheim, Roche, Pfizer

CAM

A group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine

US National Center for Complementary and Alternative Medicine

CAM use in different IBD populations

Winnipeg 57% Cork 31% Stockholm 32%
Los Angeles 68% Overall average: 51%
Predictors use:
Single, LA, Wpg, increase use of 2.7%/M.D. visit

Subjects were more likely to use CAM if:
-were not satisfied with conventional therapy,
-viewed hospitals as dangerous places,
-thought that alt med practitioners should have a role in hospitals
-felt their medical situation was hopeless.

Rawsthorne Am J GI 1999

CAM use in different IBD populations

New Zealand

Population-based (n=1291)

Prior year use of CAM 44%

No diff vs controls

Predictors of use: Female and higher education

Koning IBDJ 2013

CAM use in different IBD populations

Norway

Population based; Inception cohort (n=517)

Use at some time over 10 y =30%

Current use= 7.5%

Regular use =3.1%

Predictors of use: Female, higher education, younger age

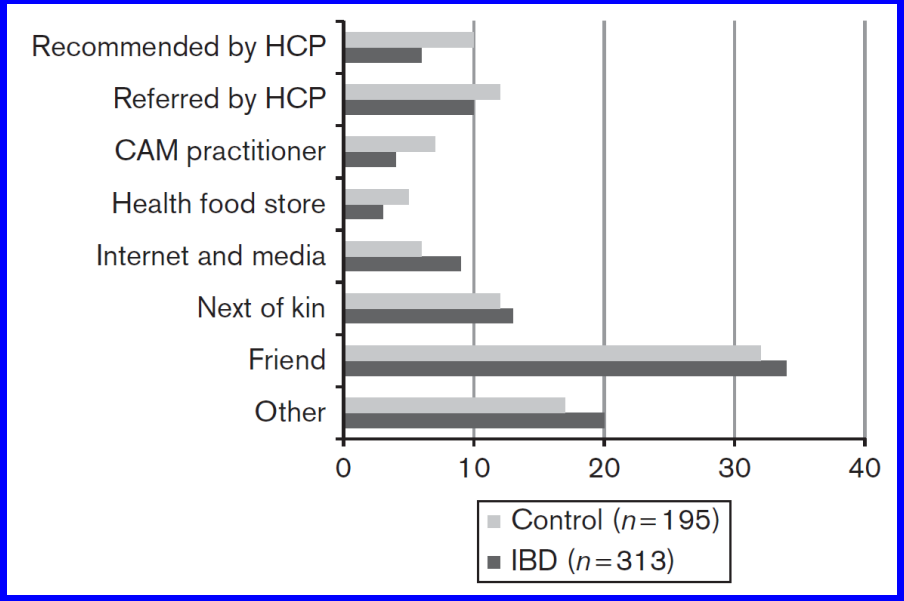
Opheim JCC 2012

CAM use in different IBD populations

Sweden

12 centre (n=648 vs controls, n=440)

48.3% v control 53.5% (p=0.025)



Oxelmark Eur J Gastroenterol Hepatol 2016

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Methods

- 12 types of CAM service providers
- 13 CAM products
- based on items from a national survey (CCHS)
- Months 0, 12, 30 and 54

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

- 74% used CAM service or product at some time
- 40% used CAM at each timepoint
- 50% used >/= 2 timepoints
- 14% used CAM consistently at every time point
- 18% of users used it for IBD

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

Most often used Service:

- **Massage (30%)**
- **Chiropractic (14%)**
- **Physiotherapy (4%)**
- **Acupuncture (3.5%)**
- **Naturopath/homeopath (3.5%)**

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

Most often used Product:

- **lactobacillus/acidophilus (8%)**
- **fish and other oils (5.5%)**
- **glucosamine (4%)**
- **chamomile (3.5%)**

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

Only predictors of CAM use

- **Sex (F>M)**
- **Lifetime hx of major depression (CIDI)**

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

Non predictors of CAM use

- Age
- Education
- Income
- Employment status
- QOL (IBDQ)
- Disease (UC vs CD)
- Disease duration
- Disease activity (MIBDI)
- Past hospitalizations or surgeries for IBD

Rawsthorne Gut 2012

The Manitoba IBD Cohort Study: Prospective longitudinal evaluation of use of CAM

Results

Non predictors of CAM use

- Other psychiatric diagnoses
- Mastery
- Perceived stress
- Heath anxiety
- Personality characteristics (NEO-FFI)
- Medication adherence (MARS)
- Beliefs about medications (BMQ)

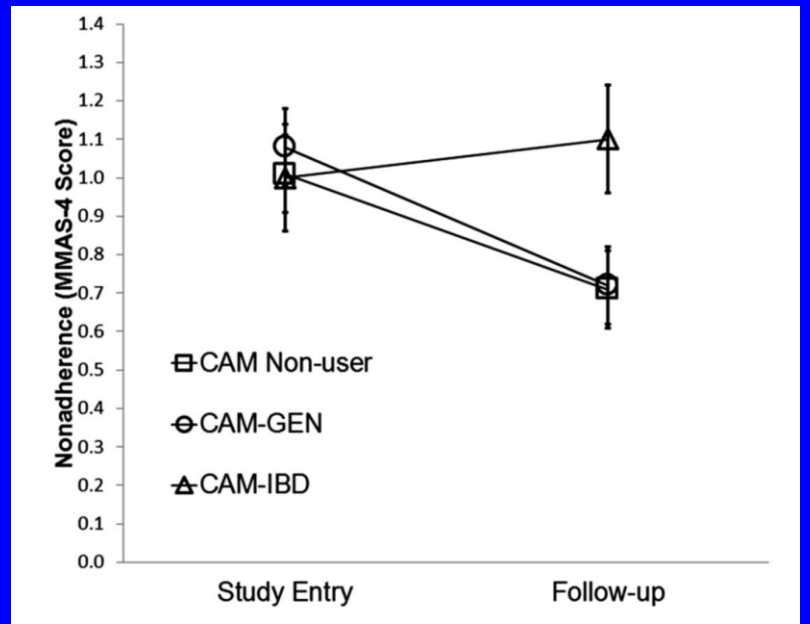
Rawsthorne Gut 2012

Is CAM just a benign add on?

- Medication adherence-Morisky (MMAS-4)
- CAM-IBD (70%) CAM-nonuse (84%, p=0.02) CAM-GEN (82%)
- Adjusted OR for adherence

CAM-IBD vs CAM-nonuse 0.47 (0.22-0.96)

CAM-GEN vs CAM-nonuse 0.85 (0.44-1.66)



Nguyen IBDJ 2016

Qualitative study on CAM use

- Sweden (n=15)
- Nurses easier to discuss than MDs
- IBD patients want to be asked about CAM
- Can be treated disparagingly if raised
- Used when conventional Rx is failing

Lindberg BMC Complement Altern Med 2014

Systematic review of RCT

- Herbal therapy in induction of remission for UC (n=11) for CD (n=4)
- Herbal therapy in maintenance of remission in UC (n=2) in CD(n=1)
- Prevent post op recurrence in CD (n=2)
- vs placebo (n=10), vs 5ASA/steroid enema (n=8), + conventional therapy (n=3)

Ng APT 2013

Systematic review of RCT

Winners:

- Aloe vera gel
- *Triticum aestivum* -Wheat grass juice
- *Boswellia serrata* gum resin (UC not CD)
- Bovine colostrum enemas
- Xilei-San suppositories
- Plantago ovata seeds (butyrate)
- *Artemisia absinthium* (wormwood)
- *Trypterygium wilfordii* (GTW)
- *Andrographis panniculata* extract
- *Curcuma longa* (Curcumin)

Ng APT 2013

Systematic review of RCT

Winners:

- Myrrh, chamomile and coffee charcoal combo
- Wheat grass juice
- Aloe vera gel
- *Artemisia absinthium* (wormwood) mixed quality
- Lifestyle modification program psych health
- Hypnotherapy risk of flare but not psych health
- Mindfulness better for those with high stress
- Moxibustion and acupuncture
- Trichuris suis ova response/not remission at 12 wks
- *Andrographis panniculata* extract
- *Curcuma longa* Curcumin

Langhorst JCC 2015

Probiotics

“live microorganisms that when administered in adequate amounts confer a health benefit on the host”

IBD Clinical and Research Centre
University of Manitoba

University of Manitoba

E coli Nissle and remitted UC

				Relapse rate
UC remission	E coli Nissle 1917	5ASA 1500 mg/d	12 wks	14% v 16%
UC remission	E coli Nissle 1917	5ASA 1500 mg/d	12 mos	36% v 34%
UC undergoing remittive RX	E coli Nissle 1917	5ASA 2400 mg/d then 1200 mg/d	12 mos	32% v 25%

VSL#3 and active UC

				Remission rate
UC active (n=147)	VSL#3 96% on 5ASA	placebo	12 wks	43% v 12% (p<0.001) 32% v 15% MH (p<0.03)
UC active (n=144)	VSL#3 All on 5ASA	placebo	8 wks	44% v 32% (p=0.13)
UC active peds (n=29)	VSL#3 Steroids +5ASA	placebo	12 mos	79% v 27%

Other probiotics and active UC

				Remission rate
UC active	***Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. *lactis BB-12***	**placebo**	**12 mos**	**8% v 25% (p=0.37)**
UC active Steroid induced remission	***Lactobacillus salivarius* subsp *Salivarius UCC118* or a *Bifidobacterium infantis 35624 (50%) on 5ASA***	**placebo**	**12 mos**	**50% v 50% unpublished**
UC active (n=20)	**bifidobacteria-fermented milk (containing a bifidobacterium and lactobacillus supplement +5ASA**	**placebo**	**12 wk**	**40% v 30%**

Probiotics and CD

- **No role in CD**
- **1 study in active CD**
- **Maintenance of remission post op-4 studies**

Lactobacillus GG, Lactobacillus johnsonii x2, VSL#3

- **Maintenance of remission-peds**

Lactobacillus GG

Curcumin

- Main active component of turmeric
- Free radical scavenger and kinase inhibitor
- Inhibit NFkB-reduce proinflammatory cytokines
- Can increase sulfasalazine levels 3.2x
- Can enhance MTX reduce liver toxicity
- Abdominal distention; N/V

Curcumin enemas-induction

- RCT; Curcumin v placebo +5ASA
- ITT; (n=45) no stat diff for response, remission, endoscopy at 8 weeks
- PP (n=30); Response 92% vs 50% (p=0.01)

  Remission 71% vs 31% (p=0.03)

  Endoscopy 85% vs 50% (p=0.04)

Singla JCC 2014

Oral Curcumin-induction

- RCT; Curcumin 3 g OD v placebo +5ASA
- 4 weeks
- ITT; (n=26 v 24)
- Remission 53% v 0% (p=0.001)
- Response , 65% v 12.5% (p<0.001)
- Endoscopy remission, 36% v 0 (p=0.043)

Lang CGH 2015

Oral Curcumin-maintenance

- RCT; Curcumin 1 g BID v placebo +5ASA
- 6 mo f/u (n=81);
- Relapse 4.7% v 20.5% (p=0.04)
- Significantly improved Endoscopic Index at 6 months

Hanai CGH 2006

RCT: Oral Curcumin v Placebo in Preventing Recurrence of Post Op CD

- AZA (2.5 mg/kg) and oral curcumin (3g/day, n=31) or an identical placebo (n=31) for 6 months
- Colonoscopy; (Rutgeerts' index score ≥i2) at month 6 (determined by central reading).
- Recurrence occurred in curcumin (58%) v placebo (68%) (P=.60).
- Severe recurrence of CD (Rutgeerts' index score ≥i3) curcumin (55%) v placebo (26%) (P=.034).
- Clinical recurrence of CD (CDAI>150) curcumin (30%) v placebo and 45% (P=.80).
- No diff in IBDQ or severe AE

Bommelaer CGH 2019

- Kedia S, Bhatia V, Thareja S, Garg S, Mouli V, Bopanna S et al. Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial. World J Gastrointest Pharmacol Ther. 2017;8(2):147

Andrographia-induction

- RCT 1200 mg A vs 4500 mg 5ASA
- N=108, 8 weeks
- Remission 21% (A) v 16% (5ASA)
- Response 76% (A) v 82% (5ASA)
- Endo remission 28% (A) v 24% (5ASA)

Tang APT 2011

Andrographia-induction

- RCT 1200 mg A vs 1800 mg A v placebo
- N=224, 8 weeks
- Response 45% (A) 60% (A) 40% (p) p<0.02
- Remission 34% (A) 38% (A) 25% (p) p=0.1
- Muc heal 38% (A) 50% (A) 33% (p) p=0.04

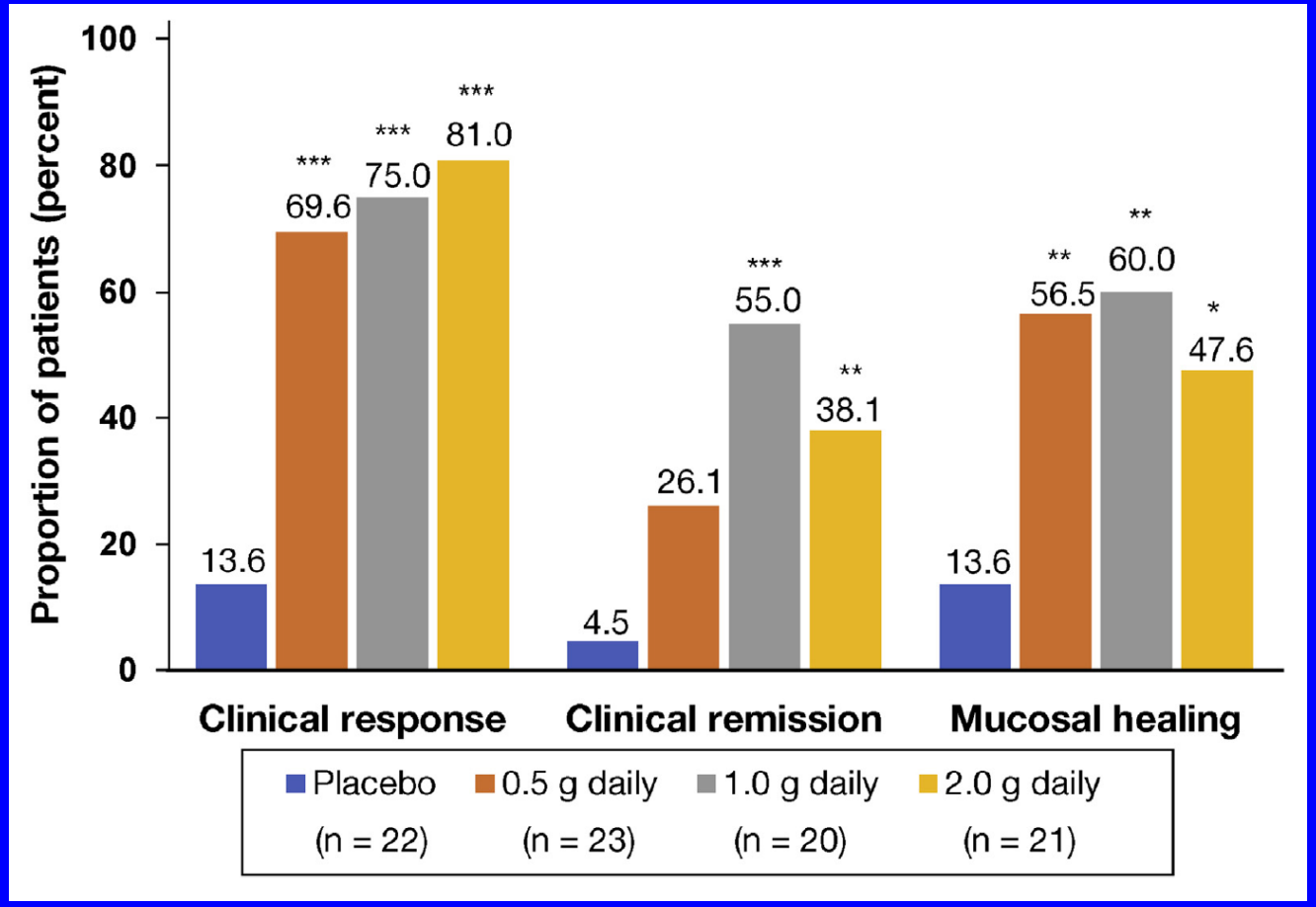
Sandborn Am J GI 2013

Indigo naturalis (Qing Dai)

- Stimulates aryl hydrocarbon receptor signalling
- Promotes IL-22 production
- 0.5g, 1g, 2g, p
- N=86
- 15.6% liver test abnormalities
- PAH in person with UC using own 2 g IN for 6 mos (not in trial)

Naganuma Gastroenterology 2018

Indigo



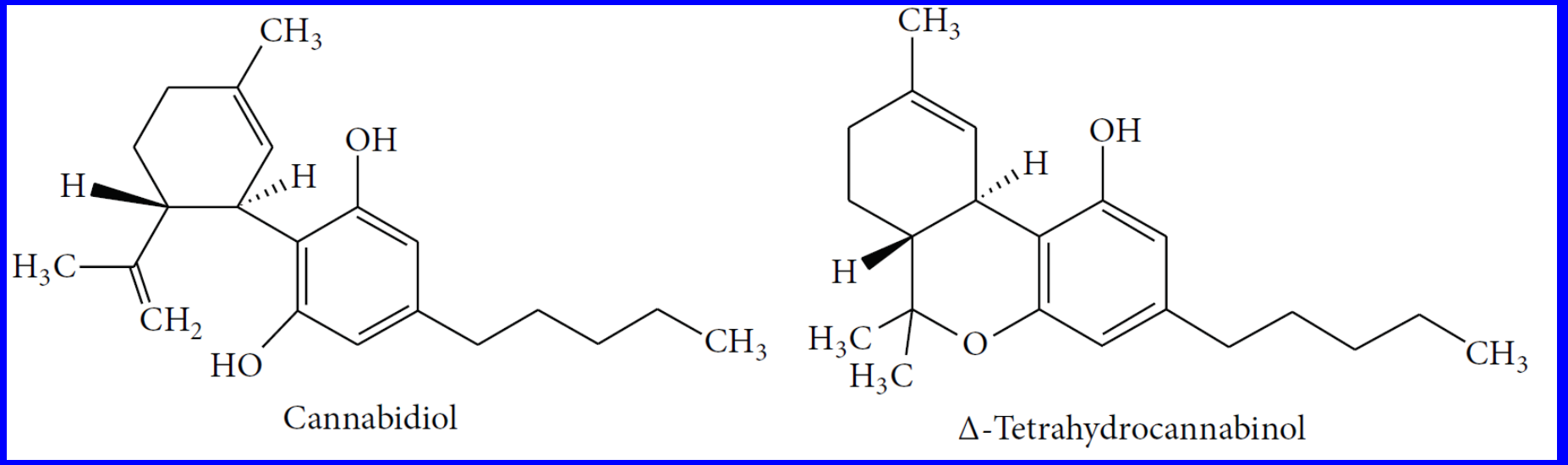
Naganuma Gastroenterology 2018

Indigo naturalis is effective even in Rx-refractory colitis: post hoc analysis from the INDIGO study

- The rates of CR were higher in IN group even in patients with steroid-dependent disease ($p < 0.001$),
- previous use of anti-TNF-α ($p = 0.002$),
- concomitant use of IM ($p = 0.013$).
- The rates of MH in IN group were significantly higher in IN group in steroid-dependent disease ($p = 0.009$).

- INDIGO AS COMPLEMENTARY OR ALTERNATIVE?.

Naganuma WJG 2019


CH3
OH
H
H
H3C
CH2
HO
CH3
Cannabidiol
CH3
OH
H
H
H3C
H3C
O
CH3
Δ-Tetrahydrocannabinol

Endocannabinoid receptors

CB1 receptors	CB2 receptors	Other EC receptors
ENS, epithelial lining, blood vessels of colon	Immunocytes, myenteric plexus neurons Absent in the brain	G protein receptor coupled receptor (GPR55)
Depresses excitatory transmitter release Leads to decrease Ach and decrease motility	Reduce pain thresholds	Transient receptor potential cation channel subfamily V member 1 (TRPV1)
Reduce gastric acid secretion		PPARα and PPARγ
Present in DVC and area postrema		
Upregulated in inflammation		
THC partial CB1/2 agonist known for psychotropic effects CBD little to no CB1 or CB2 affinity has anti-inflammatory and immunomodulatory effects		

When did CBD, the voguish cannabis derivative, go from being a fidget spinner alternative for stoners to a mainstream panacea (sic).

- **Maybe it was in January, when Mandy Moore, hours before the Golden Globes, told Coveteur that she was experimenting with CBD oil to relieve the pain from wearing high heels. “It could be a really exciting evening,” she said. “I could be floating this year.”**

Alex Williams NY Times Oct 27 2018

- **Maybe it was in July, when Willie Nelson introduced a line of CBD-infused coffee beans called Willie's Remedy.**
- **Or maybe it was earlier this month, when Dr. Sanjay Gupta gave a qualified endorsement of CBD on "The Dr. Oz Show." "I think there is a legitimate medicine here," he said. "We're talking about something that could really help people."**

Alex Williams NY Times Oct 27 2018

“Among beauty products alone, CBD has already achieved cliché status, popping up in blemish cream, sleeping masks, shampoos, hair conditioners, eye serums, anti-acne lotions, mascaras, massage oils, soaps, lip balms, bath bombs, anti-wrinkle serums, muscle rubs and a Sephora aisle’s worth of moisturizers, face lotions and body creams. Even the bedroom is not safe from the CBD invasion, to judge by the spate of CBD sexual lubrucants on shelves.”

NY Times Oct 27 2018

- **In June, 2018, the FDA approved a cannabidiol-based drug called Epidiolex as a treatment for severe forms of epilepsy, representing the first government-sanctioned medical use of CBD oil.**

NY Times Oct 27 2018

Prevalence of MJ use

- **~20%, US-wide report using in the past 30 d**
- **~4-6% use daily or almost daily. This suggests 20-25% of adolescents who do use cannabis, use it habitually, an increasing trend over the past 10 years.**
- **Steady decline in perception of risk with regular use. Regular use of cannabis is perceived as not having great risk by 60% of high school seniors, increasing since 2004.**
- ***20% of users meet def'n for cannabis use disorder***

Schuermeyer Drug Alc Depend 2014 Hasin Neuropsychopharacol Rev 2018
Johnstone Nat Instit on Drug Abuse at the NIH 2016.

NHANES IBD vs controls

- **MJ/hash use 67% v 60% (OR 1.37, 1.37-1.38)**
- **Onset of use 15.7 y vs 19.6 y**
- **>/= 3 joints/d 65% vs 20% (OR 7.97, 7.9-8.05)**

Weiss Drug Alc Depend 2015

1666 participants CCFA Partners

- 4.4% using prescribed marijuana
- 14% lived where both medical and recreational marijuana is legal
- Of 14%, 21% reported recreational marijuana specifically for IBD
- 12.8% asked their MD about use
- Users reported positive benefits (81%), but users also reported more depression, anxiety, pain interference, and lower social satisfaction than non-users.

Kerlin DDS 2018

201 Manitobans surveyed on Lifestyle

Aims:

- **To determine what % of IBD use cannabis to treat IBD-related sx vs recreationally.**
- **To assess risk factors for substance use in individuals with IBD using cannabis to manage their IBD symptoms.**
- **To determine whether the prevalence of substance misuse risk factors differed between medicinal versus recreational users.**

Hansen IBDJ 2020

201 Manitobans surveyed on Lifestyle

46% never used cannabis.

Users (n=108): 59% CD, 52% UC

43% of users used to Rx IBD sx

(CD 53%, UC 28%)

Medicinal users:

Higher pain disability index

More likely to use for coping;

Less likely to get “high”

Hansen IBDJ 2020

More likely to score high on impulsivity

More likely to have higher depression scores

201 Manitobans surveyed on Lifestyle

Recreational users were more likely to use it for social reasons (p=0.014).

predictors of using cannabis to Rx IBD sx (LRA)

smokers 4.1X

those with moderate-severe depressive sx 3.7x

score above the median on impulsivity as measured by the SURPS 4.1x

Hansen IBDJ 2020

MJ Issues

- Increase in potency of THC content in marijuana from 3% (1980s) to 12% (2012) may potentiate adverse effects.
- Cannabis ingested in an edible form is more difficult to titrate, unlike vaping or inhaling, as the effect may be delayed, and therefore higher doses may be consumed leading to intoxication.
- Heavy use may cause impaired memory for >1 week after abstinence, hyperemesis and W/D sx
- Addiction risk may be higher for those beginning heavy use in adolescence, and this behavior may predict progression to harder drugs.

Volkow NEJM 2014, Santaella-Tenorio Am J Pub Health 2017, Wang CMAJ 2008.

Addiction; Adverse effects

- **Prolonged use of Cannabis has shown neurological changes in adolescents including a decrease in gray matter volume in certain brain areas** ***Battistella Neuropsychopharmacology 2014***
- **Population-based studies have demonstrated an increased risk for MVA** ***Li Epidemiol Rev 2012***
- **Cannabis hyperemesis syndrome**
- ***Allen Gut 2004, Wang CMAJ 2008***

MJ Issues

- **American Academy of Pediatrics and the Academy of Child and Adolescent Psychiatry oppose marijuana legalization.**

Pediatrics 2015;135:584-7.

AACAP Marijuana Legalization Policy Statement: Committee on Substance Abuse American Academy of Child and Adolescent Psychiatry, 2014.

HRQOL

Study	Instrument	THC Sample	Comp Sample	Effect Size (95%CI)	
Johnson 2010	QLQ-C30 - global health status	49	51	0.05 (-0.35 to 0.44)	Cancer Pain
Johnson 2012	QLQ-C30 - global health status	49	51	0.12 (-0.27 to 0.51)	
Fiz 2011	SF-36 (physical health composite)	28	28	-0.09 (-0.61 to 0.44)	Fibromyalgia
Fiz 2011	SF-36 (mental health composite)	28	28	0.28 (-0.25 to 0.81)	
Korthius 2008	Modified SF-36 (mental health composite)	905	905	-3.43 (-3.58 to -3.29)	HIV
Korthius 2008	Modified SF-36 (physical health composite)	905	905	-1.45 (-1.55 to -1.34)	
Sherbourne 2000	MOS-QoL (mental health composite)	341	1407	0.11 (0 to 0.23)	
Sherbourne 2000	MOS-QoL (physical health composite)	341	1407	0.42 (0.3 to 0.54)	
Lahat 2012	EQ-5D (index score)	13	*	2.04 (1.09 to 2.98)	IBD
Pini 2012	SF-36 (mental health composite)	26	26	0 (-0.54 to 0.54)	Med Overuse Headache
Pini 2012	SF-36 (physical health composite)	26	26	0 (-0.54 to 0.54)	
Svendsen 2004	SF-36 (physical health composite)	12	12	0.09 (-0.71 to 0.89)	MS
Svendsen 2004	SF-36 (mental health composite)	12	12	0.21 (-0.59 to 1.02)	
Flachenecker 2014	EQ-5D (index score)	50	*	0.13 (-0.26 to 0.52)	
Flachenecker 2014	MSQoL-54 (mental health composite)	50	*	0.36 (-0.02 to 0.73)	
Flachenecker 2014	MSQoL-54 (physical health composite)	50	*	0.38 (-0.02 to 0.79)	
Bestard 2010	SF-36 (mental health composite)	49	52	0.01 (-0.39 to 0.4)	Neuropathic Pain
Bestard 2010	SF-36 (physical health composite)	49	52	0.06 (-0.33 to 0.45)	
Bestard 2010	EQ-5D (index score)	49	52	0.11 (-0.28 to 0.5)	
Ware 2010	EQ-5D (index score)	6	5	0.08 (-1.11 to 1.27)	
	Between-Subject Effects	1416	2486	0.05 (-0.34 to 0.44)	Median
	Within-Subject Effects	244	*	0.35 (-0.2 to 0.9)	

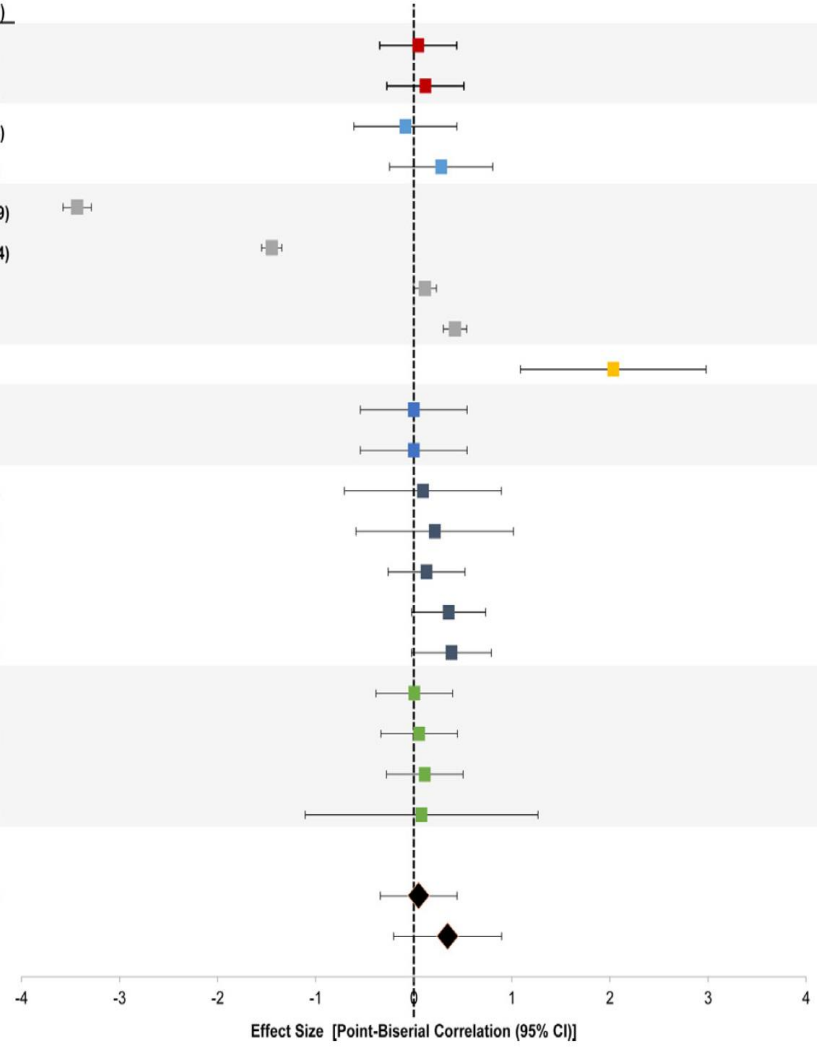


Fig. 2. Meta-Analysis Results: The Effect of Cannabis and Cannabinoids on HRQOL.

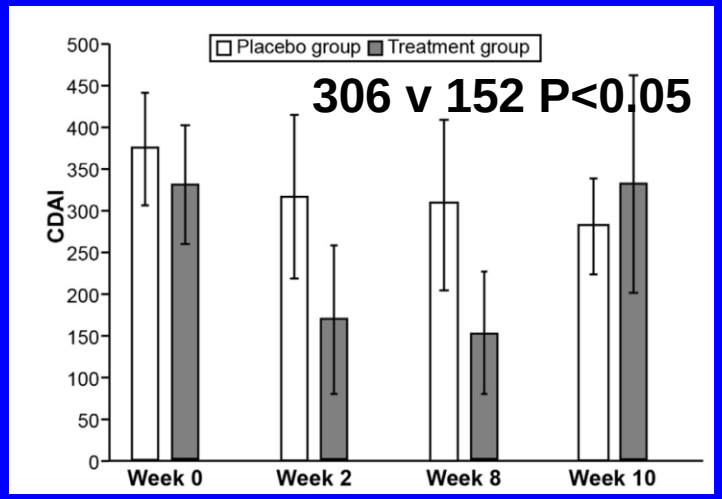
THC in chronic pain
RCT vs placebo

- 3 months of chronic pain post op or chronic pancreatitis
- THC 9 mg x 5d, 15 mg x 5d, 24 mg x 40d
- 65 subjects; VAS pain
- NO DIFFERENCES in:
- VAS (40% vs 37% improvement)
- Global impression of pain, pain catastrophizing, pain related and generalized anxiety, QOL, alertness, mood, psychedelic effects
- Decreased appetite, dizziness, dry mouth, nausea

De Vries CGH 2017

MJ in CD
RCT vs placebo

- N=21, CDAI >200, 8 wks
- Cigarettes BID; THC vs cannabis flowers (no THC)
- CDAI <150 5/11 vs 1/10 (p=0.43)
- CDAI decrease >100 10/11 vs 4/10 (p=0.028)

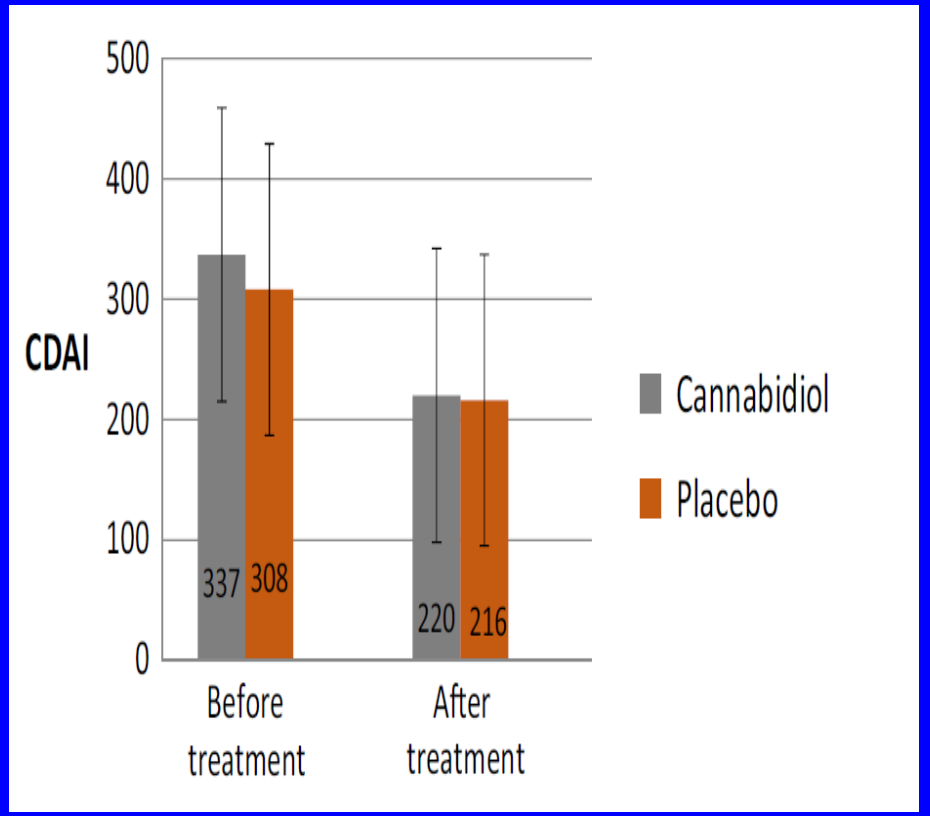


- Most knew if on THC or placebo
- Side effects similar

Naftali CGH 2013

CBD in CD

- RCT; n=20; 8 wks
- 10 mg BID vs placebo
- 11/20 failed anti TNF
- No difference in SE



Naftali DDS 2017

“Complementary”

- Only properly conducted studies will advance the use of CAM
- Studies should use agents as complementary agents rather than for primary therapy