Cannabis Research and its medical potential

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Disclosures and thanks for support

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CAMH
CIHR
NIH-NIDA and the NIDA drug supply program and NIH-NIAAA

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Ontario Ministry of Innovation, Canadian Fondation for Innovation, Canadian Tobacco Control Research Initiative
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Pfizer Cardio-vascular Research Award
OPGRC, Ontario Lung Association, Heart and Stroke Foundation
Narsad, MITACS, PSI Foundation

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Grant support from Pfizer, Bioprojet, Alkermes (underway), Canopy Health Innovation, ACS
In kind support from GW Pharma and Brainsway, Aurora, Canopy

Objectives

1. Description of the cannabinoid system
2. Importance of approaching research with an open mind
3. Presenting some of the challenges to perform research on cannabis

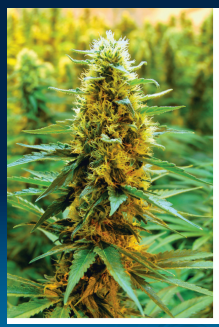
Prescription cannabinoids

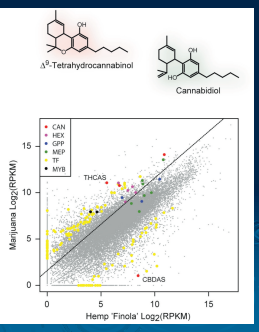
Dronabinol (Δ-9 tetrahydrocannabinol – THC) (2.5 - 10mg)
- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting and anorexia associated with HIV/AIDS**

Nabilone (0.25 - 1.0mg)
- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting**

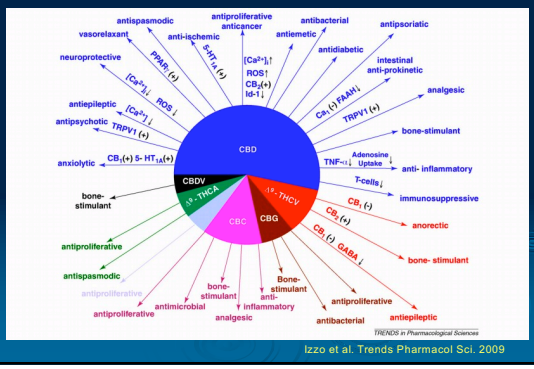
Nabiximols (2.7mg THC + 2.5mg CBD)
- Oromucosal spray
- Approved in Canada for **multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain**

Delta 9 Tetrahydrocannabinol and Cannabidiol are the two main components of cannabis





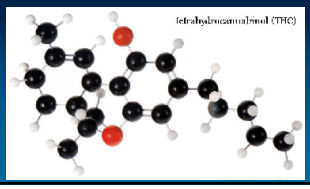
Non-psychoactive phytocannabinoids

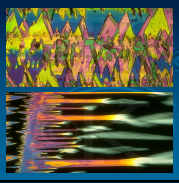


Izzo et al. Trends Pharmacol Sci. 2009

Delta-9-tetrahydrocannabinol (THC) is the main active ingredient in cannabis

- Chemical structure elucidated about 40 years ago (Gaoni and Mechoulam, 1964 *J Am Chem Soc)*
- It was only after another 25 to 30 years passed that high-affinity binding sites for THC and its synthetic analogs were described and two types of G protein-coupled cannabinoid receptors were cloned and characterized (CB_1,Matsuda et al 1990 Nature; CB_2 Munro et al 1993 Nature)



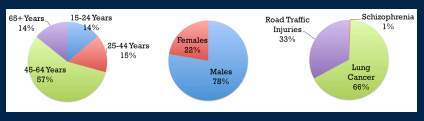


The endogenous cannabinoid system and its receptors

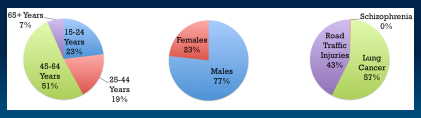
- Currently are two cloned and characterized subtypes of cannabinoid receptors, **CB_1** and **CB_2**
- **CB_1 receptors** are localized mainly in the central nervous system (**CNS)** and are thought to mediate most central effects of THC and its synthetic analogs and their liability for abuse
- **CB_2** receptors are primarily localized in peripheral organs and are involved in modulation of immune functions, but have been recently identified in the CNS where their functions remain to be elucidated
- Naturally occuring endogenous ligands for these receptors exist as well as metabolic enzymes that can rapidly inactivate them (FAAH anandamde and MAGL for 2-AG)

Burden of disease

- 287 cannabis-attributable deaths (95% CI: 108 – 609)



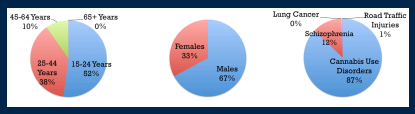
10,533 cannabis-attributable years of life lost (95% CI: 4,760 – 20,833)



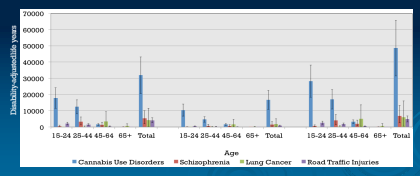
From Imtiaz et al, 2016

CUD>Driving>others

- 55,813 cannabis-attributable years lived with disability (95% CI: 38,175 – 74,094)



66,346 cannabis-attributable disability-adjusted life years (95% CI: 47,785 – 87,207)



From Imtiaz et al, 2016

Cannabis

1) Cannabis and Addiction
2) Cannabis and Weight
3) Cannabis and Driving

Why Do People Start to Take Cannabis?

To feel good

To have novel:
- feelings
- sensations
- experiences
- AND

to share them

To feel better

To lessen:
- anxiety
- worries
- fears
- depression
- Hopelessness
- PAIN

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- •PAIN

RECREATIONNAL USE vs MEDICAL USE

Cannabis as a typical Addictive Substance

- There is no more debate on the fact that cannabis is addictive
- Cannabis Withdrawal syptoms are very well characterized now and in the DSM (ex irritability, anxiety, restlessness, appetite and sleep disturbances…) Thanks to the work of Dr Budney and others
- 8 – 9 % of ever users will develop cannabis dependence, an ever larger fraction will develop cannabis use disorder
- Addictive potential lower than alcohol, much lower than opiate or psychostimulant drugs

14

Risks factors for Cannabis Use Disorder

- Initiation of use by age 15
- Low socioeconomic status
- Personal or peer use of other drugs and tobacco
- Regular cannabis use
- Anti-social behaviour
- Living alone
- Using cannabis as a coping mechanism
- Recent life events/trauma history
- Availability
- Lack of knowledge of risk
- Norm misperceptions
- Concurrent mental health disorders
- Poor parental monitoring and supervision
- Low family bonding, high family conflict
- Academic failure
- Lack of school engagement
- Lack of involvement in community/ religious organizations
- Gender

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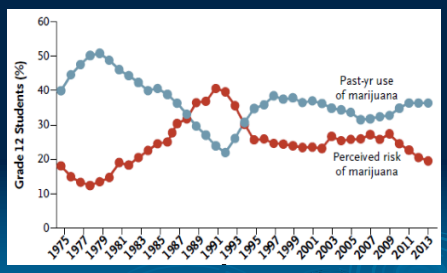
15

Perceived Risk and Use



Source: Volkow, Baler, Compton, & Weiss, 2014; reproduced with permission, Massachusetts Medical Society

16

How to define Cannabis Use Disorder ?

Cannabis Use Disorder is the clinical term for a problematic pattern of cannabis use leading to clinically significant impairment or distress. Based on the number of criteria present, it can range , ranging from mild to severe (addiction). Individuals must show at least two symptoms over a 12-month period to receive the diagnosis. Symptoms of Cannabis Use Disorder can include:

- Cannabis is often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
- A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
- Craving, or a strong desire or urge to use cannabis.
- Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
- Recurrent cannabis use in situations in which it is physically hazardous.
- Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
- Tolerance (need for markedly increased amounts of cannabis to achieve desired effect or markedly diminished effect with continued use of the same amount of cannabis.
- Cannabis withdrawal

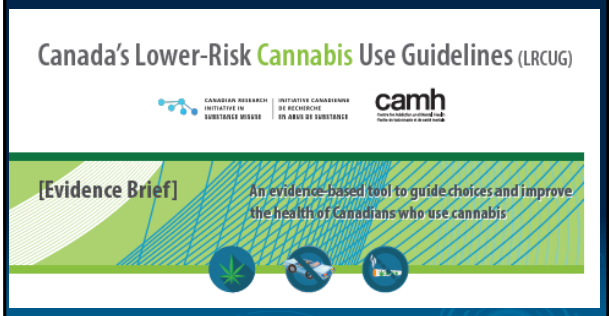
17

Symptoms associated with CUD

- 91% experienced persistent desire for cannabis;
- 84% reported unintentional use of cannabis;
- 74% experienced symptoms of withdrawal;
- 74% reported spending excessive time obtaining and using cannabis;
- 63% reported continued use of cannabis despite experiencing health problems;
- 21% experienced tolerance; and
- 18% experienced negative social consequences as a result of their use.

From Coffey et al, 2002, from an Australian Cohort. 7% of users were dependent

How to prevent CUD ?



From Fischer et al, 2017

Lower-risk cannabis use guidelines

- The health harms of cannabis are associated with a number of factors that are potentially modifiable
- Risk of harm can be greatly reduced if:
  - use is delayed until early adulthood
  - frequent use is avoided
  - users shift away from smoking cannabis towards less harmful (smokeless) delivery systems
  - less potent products are used
  - people with higher risk of cannabis-related problems (e.g. a personal or family history of psychosis) consider abstaining altogether

Source: *Fischer et al.*

What treatment appraoches are effective ?

- Screening :importance of asking about cannabis use
- Assessment : importance of asking the DSM criteria which will then allow to put a diagnosis of CUD and rate severity based on the number of criteria presents. Motives of uses, Paying attention to underlying MI and other co-addictions…. General principles of Addiction Medicine are used
- Treatment goals; Usually Abstinence is the preferred option. Harm reduction principles.
- Importance of using Evidence-Based Approaches. Utility of Cochrane Collaborative group to review the literature: interventions can be presented in two main categories: Psycho-social and Pharmacological interventions

How to treat CUD ?

Psychosocial interventions for cannabis use disorder (Review)

Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L

THE COCHRANE COLLABORATION®

Gates et al., 2016 Cochrane Review

Types of Psychosocial interventions

- **Cognitive behavioural therapy (CBT)**
- **Motivational interviewing/ motivational enhancement therapy (MET)**
- Components of cognitive and motivational approaches delivered with a focus on the importance of obtaining social support (SS)
- Drug counselling and/or education (DC)
- Contingency management (CM)
- Mindfulness-based meditation (MM)
- Relapse prevention (RP)
- Combination of the above

How to treat CUD ?

Pharmacotherapies for cannabis dependence (Review)

Nielsen S, Gowing L, Sabioni P, Le Foll B

No Pharmacological treatment available !

Cochrane Library

Cochrane Database of Systematic Reviews

Nielsen et al,2019

How to treat CUD ?

Incomplete evidence for all of the pharmacotherapies investigated;

Little value in the treatment of CUD: SSRI antidepressants, mixed action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone) and norepinephrine reuptake inhibitors (atomoxetine)

Weak evidence base for the anticonvulsant gabapentin and the glutamatergic modulator N-acetylcysteine and oxytocin

Potential value of THC preparations, but the limited evidence, should be considered still experimental

Use of Nabiximols (THC/CBD) as a possible substitution therapy for cannabis dependence ?

- Developed by GW Pharmaceutical
- *Sativex® is a cannabinoid medicine used in the treatment of spasticity due to multiple sclerosis. Explored for pain*
- Each 100 µl spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD)

Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Drug and Alcohol Dependence 161 (2016) 298–306

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings

Jose M. Trigo[a], Dina Lagzdins[a], Jürgen Rehm[b,c,d,e,f], Peter Selby[e,g,h], Islam Gamaleddin[a,i,j], Benedikt Fischer[b,e,k], Allan J. Barnes[l], Marilyn A. Huestis[l], Bernard Le Foll[a,g,*]

Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Demographics

Characteristics	Completers $n=9$
Demographics, no. (%)	
Age, years, mean (SD)	35.9 (11.5)
Male	8 (88.9%)
White, Non-hispanic	9 (100%)
Latin American	0 (0%)
Aboriginal	0 (0%)
Mixed	0 (0%)
College degree	4 (44.4%)
Full-time employed	1 (11.1%)
Married	1 (11.1%)

Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Inclusion Criteria

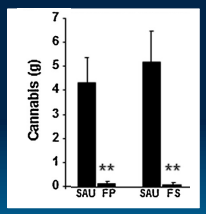
- age 18-50 ; current cannabis dependence
- cannabis as primary drug of abuse
- frequent cannabis use (i.e., at least 5 days per week)
- experienced at least 2 withdrawal symptoms during previous cessation periods
- cannabis use not for medical purposes
- not seeking treatment for cannabis dependence

Exclusion Criteria

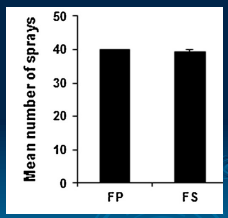
- psychiatric disorder
- history of seizures
- sensitivity to Dronabinol, Cannabidiol, Propylene glycole, Ethanol or peppermint oil
- unstable medical condition
- physical dependence on any other drugs (excluding nicotine)
- current psychotropic medication other than treatment of insomnia
- pregnant or breast-feeding
- job that involves operating heavy machinery
- family history of psychotic symptoms

Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Cannabis use



Sativex use

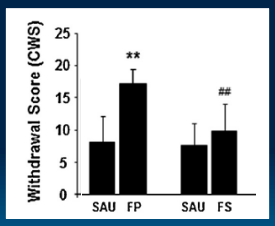


SAU: Smoke as Usual
FP: Fixed Placebo
FS: Fixed Sativex

J.M. Trigo et al. / Drug and Alcohol Dependence 161 (2016) 298–306

Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Cannabis withdrawal



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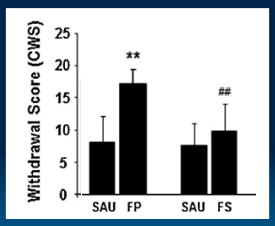
Impact of Nabiximols (THC/CBD) on Cannabis Withdrawal

Cannabis withdrawal



SAU: Smoke as Usual
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No Impact on Cravings

J.M. Trigo et al. / Drug and Alcohol Dependence 161 (2016) 298–306

Use of Nabiximols (THC/CBD) as a possible substitution therapy for cannabis dependence ?

RESEARCH ARTICLE

Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial

Jose M. Trigo[1], Alexandra Soliman[1], Lena C. Quilty[2,3], Benedikt Fischer[3,4,5,6], Jürgen Rehm[3,4,5,7,8], Peter Selby[3,9,10], Allan J. Barnes[11¤a], Marilyn A. Huestis[11¤b], Tony P. George[3,9,12], David L. Streiner[3,13], Gregory Staios[1], Bernard Le Foll[1,9,*]

PLOS ONE

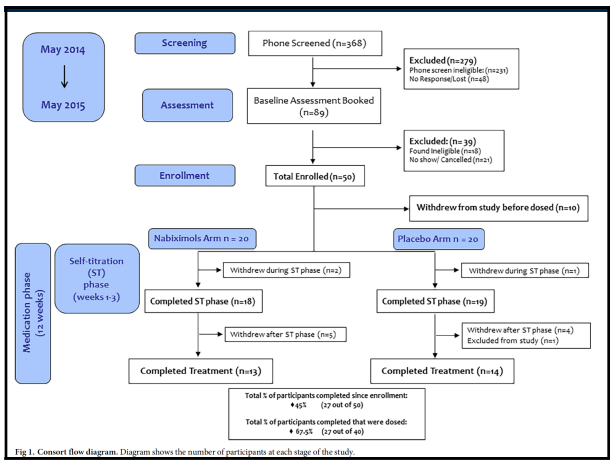
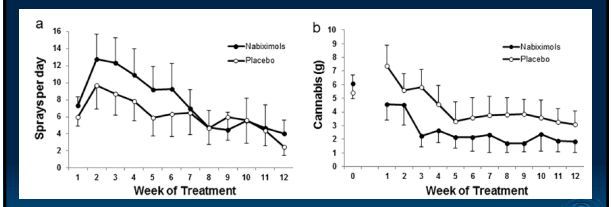


Fig 1. Consort flow diagram. Diagram shows the number of participants at each stage of the study.

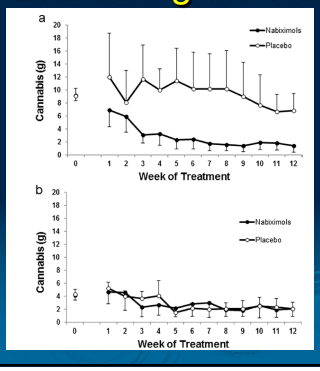
Use of nabiximols and of cannabis during the trial



Use of nabiximols and of cannabis during the trial

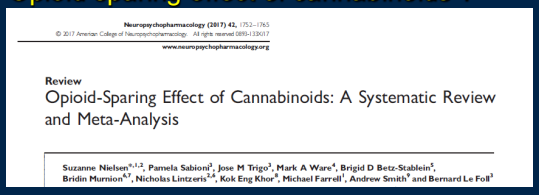
High Sprays users

Low Spray users



Beyond Cannabis

- 'Opioid sparing effect of cannabinoids ?



Neuropsychopharmacology (2017) 42, 1752–1765
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www.neuropsychopharmacology.org

Review

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen[1,2], Pamela Sabioni[2], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,8], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

Beyond Cannabis

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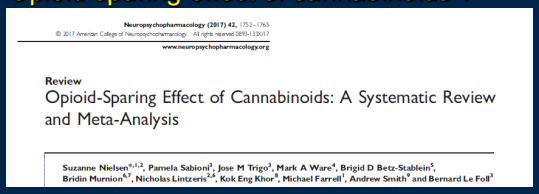

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Review

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

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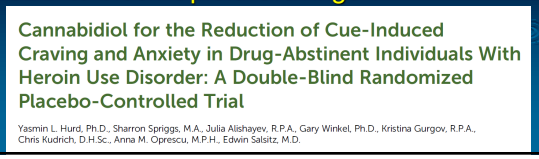
- CBD to block Opioid Cravings ?



Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial

Yasmin L. Hurd, Ph.D., Sharron Spriggs, M.A., Julia Alishayev, R.P.A., Gary Winkel, Ph.D., Kristina Gurgov, R.P.A., Chris Kudrich, D.H.Sc., Anna M. Oprescu, M.P.H., Edwin Salsitz, M.D.

Beyond Cannabis

- CBD to reduce Drinking ?

Experimental and Clinical Psychopharmacology

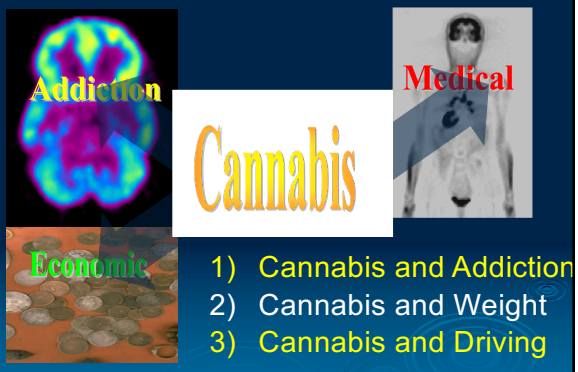
Effects of Cannabidiol on Alcohol-Related Outcomes: A Review of Preclinical and Human Research

Christina N. Nona, Christian S. Hendershot, and Bernard Le Foll

Online First Publication, May 23, 2019. http://dx.doi.org/10.1037/pha0000272

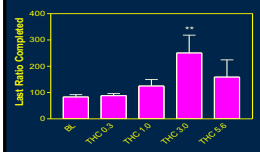
Addiction Summary

- Cannabis is addictive
- Cannabis Use Disorders prevention: LRCUG
- CUD Treatment: Effective behavioral treatments are available. Currently no approved pharmacotherapies for the treatment of CUD.
- Cannabinoid drugs may have therapeutic properties: THC/CBD mixture for CUD treatment ? FAAH Blocker promising alternative. Cannabinoid blockers (neutral antagonist, allosteric modulators, still experimental)
- Cannabinoid drugs (THC and/or CBD) may have utility for opioid crisis: possible opioid sparing.
- CBD potential as Anti-addictive agent

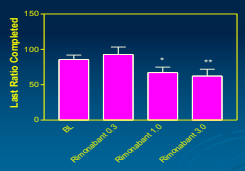


1) Cannabis and Addiction
2) Cannabis and Weight
3) Cannabis and Driving

Cannabinoids and the motivation to respond for food in rats



- THC increases the motivation to respond for food



- The CB1 antagonist Rimonabant decreases the motivation to respond for food

Solinas and Goldberg, 2005 *Neuropsychopharmacology*

Rimonabant is a medication for obesity and metabolic risk factors

Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study

*Luc F Van Gaal, Alla M Rissanen, André J Scheen, Olivier Ziegler, Stephan Rössner, for the RIO-Europe Study Group**

Lancet 2005; 365: 1389–97

Rimonabant is a medication for obesity and metabolic risk factors

Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients
RIO-North America: A Randomized Controlled Trial

F. Xavier Pi-Sunyer, MD
Louis J. Aronne, MD
Hassan M. Heshmati, MD
Jeanne Devin, MS
Julio Rosenstock, MD
for the RIO-North America Study Group

JAMA. 2006;295:761-775

Rimonabant is a medication for obesity and metabolic risk factors


The NEW ENGLAND JOURNAL of MEDICINE

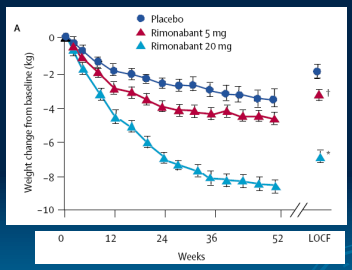
ORIGINAL ARTICLE

Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia

Jean-Pierre Després, Ph.D., Alain Golay, M.D., and Lars Sjöström, M.D., Ph.D., for the Rimonabant in Obesity–Lipids Study Group*

N ENGL J MED 353;20 WWW.NEJM.ORG NOVEMBER 17, 2005

Rimonabant is a medication for obesity and metabolic risk factors



Van Gaal *et al*, 2005

Cannabis and food intake – the two go hand in hand!

http://metro.co.uk/2016/03/07/7-really-surprising-health-benefits-from-smoking-cannabis-5738619/

http://movesmart.org/author/joy-nalywalko/

Cannabis and food intake – the two go hand in hand!

Few years ago, we realize that no study had evaluated the impact of cannabis use on weight in the general adult population. Are cannabis users obese?

The NESARC

- Conducted by the NIAAA
  - *National Institute on Alcohol Abuse and Alcoholism*
- Face to face interviews

Chart Flow

53,201 randomized participants

10,108 declined

43,093 participants

→Population based national representative sample

Cannabis use

- During the last 12 months, about how often did you use marijuana?"
  - (i) Every day
  - (ii) 5 to 6 days a week,
  - (iii) 3 to 4 days a week,
  - (iv) 1 to 2 days a week,
  - (v) 2 to 3 days a month
  - (vi) once a month or less
  - (vii) Never

Cannabis use in the last 12 months

- (iv) 3 days a week to everyday
- (iii) at least once a month to twice a week
- (ii) at least once a year but less than once a month
- (i) no use in the last 12 months

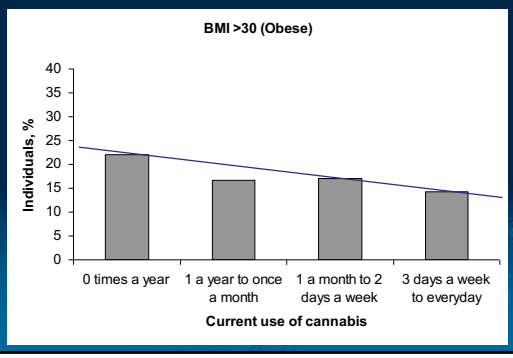
Body mass index

- BMI=(weight in Kg) /[height (m)]^2
- Obesity=BMI >30.0 kg/m2 (N= 9,879)

Other variables considered

- Past 12-month cigarette use
- Race
- Age
- Educational level
- Marital status

Cannabis use and obesity in the NESARC



Cannabis use and obesity in the NESARC

Cannabis use frequency	Odds ratio	AOR[a] (95% CI)	AOR[b] (95% CI)
No use in the past 12 months	1	1	1
More than once a year, less than once a month	0.71 (0.54-0.92)	0.76 (0.58-0.98)	0.82 (0.63-1.05)
Once a month to 2 days a week	0.73 (0.57-0.93)	0.77 (0.60-0.98)	0.79 (0.62-1.01)
3 days a week to everyday	0.59 (0.44-0.79)	0.63 (0.47-0.84)	0.61 (0.46-0.82)

Abbreviation: CI, confidence interval.
All analyses are weighted to reflect national population estimates.
a Adjusted for sex and age.
b Adjusted for sex, age, race/ethnicity, educational level, marital status, region and tobacco smoking status.

Major confounding factor: Tobacco smoking

- We conducted the same analysis after the exclusion of past-year tobacco smokers.
  - →Results almost identical

Main limitations

- Informations based on self-reports
  - No confirmation by direct measurement.
  - Self reports tend to underestimate BMI.
- Obese participants in the NESARC may avoid cannabis because of its effect on weight.
- Biological substrates underlying those effects are unclear.
- Above all: False positive
  - Need to be replicated in an independent sample

The NCS-R sample

- Independent survey of 9,282 respondents (response rate, 73.0%)
- Conducted by the National Institute of Mental Health Collaborative Psychiatric Epidemiology Surveys (CPES) from 2001–2003.

Cannabis use in the last 12 months

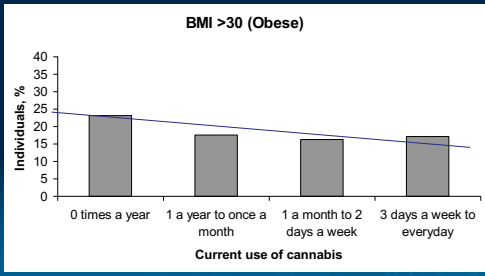
- (iv) 3 days a week to everyday
- (iii) at least once a month to twice a week
- (ii) at least once a year but less than once a month
- (i) no use in the last 12 months

→EXACTLY like in the NESARC

Body mass index

- BMI=(weight in Kg) /[height (m)]^2
- Obesity=BMI >30.0 kg/m2 (N= 9,879)

Cannabis use and obesity in the NCS-R



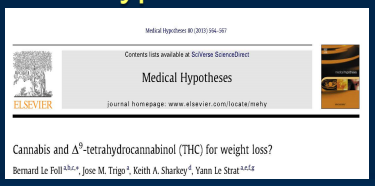
Obesity rates are lower in frequent cannabis users!

Frequency of Cannabis Use	Obesity rate
No use in the past year	22-25 %
≥ 3 Days per week	16-17 %

>50,000 respondents across 2 nationally representative US studies

Le Strat and Le Foll. Am J Epidemiol 174, 929-933 (2011)

Cannabis and obesity: a hypothesis


Medical Hypotheses 80 (2013) 564–567

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Cannabis and Δ^9-tetrahydrocannabinol (THC) for weight loss?

Bernard Le Foll[a,b,c,*], Jose M. Trigo[a], Keith A. Sharkey[d], Yann Le Strat[e,f,g]

THC blocks endogenous agonists from binding to cannabinoid CB_1 receptors during high fat food-induced high endocannabinoid tone

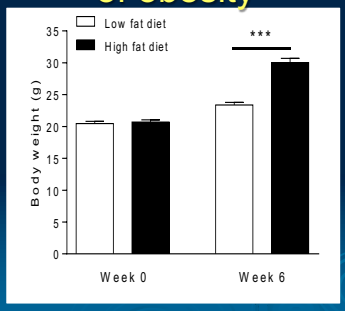
Le Foll et al., Medical Hypotheses 80, 564-567 (2013)

What are the effects of chronic THC in mice?

- Male mice
- High-fat diet (45% calories from fat) or mouse chow (13% calories from fat) for 6 weeks
  - Lean or Diet-induced obese (DIO)
- Daily treatment with THC – 2mg/kg for 3 weeks or 4mg/kg for 1 week.
- Measure locomotion, GI transit, food intake, body weight and cecal microbiota

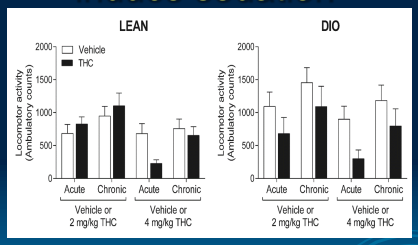
Cluny et. al., PLoS One, 10, e0144270 (2015)

Development of a mouse model of obesity



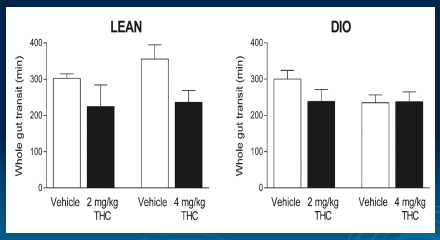
Cluny et. al., PLoS One, 10, e0144270 (2015)

Chronic THC does not induce sedation



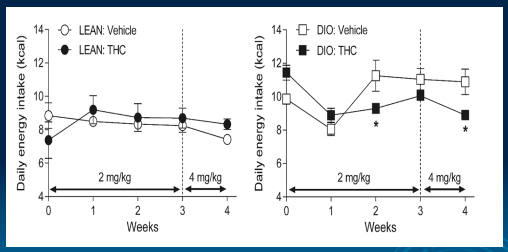
Cluny et. al., PLoS One, 10, e0144270 (2015)

Chronic THC does not alter gastrointestinal transit



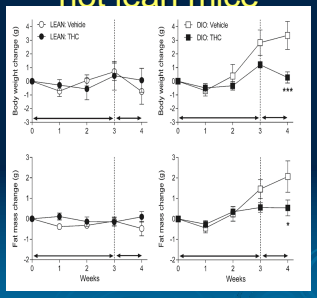
Cluny et. al., PLoS One, 10, e0144270 (2015

Chronic THC reduces food intake in obese, but not lean mice



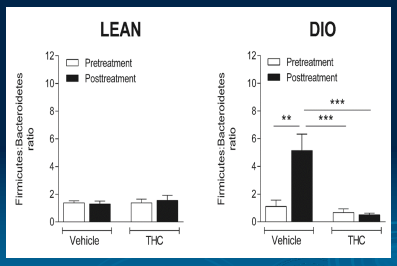
Cluny et. al., PLoS One, 10, e0144270 (2015)

Chronic THC prevents weight gain and fat accumulation in obese, but not lean mice



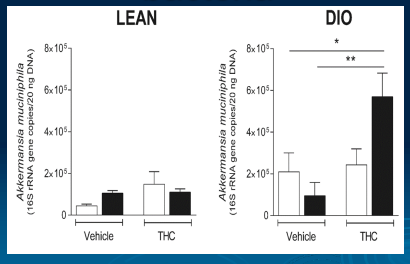
Cluny et. al., PLoS One, 10, e0144270 (2015)

Chronic THC prevents high fat diet-induced changes in gut microbiota in obese, but not lean mice



Cluny et. al., PLoS One, 10, e0144270 (2015)

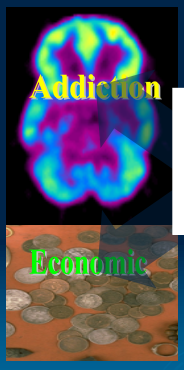
Chronic THC increases weight loss-promoting "beneficial" gut bacteria



Cluny et. al., PLoS One, 10, e0144270 (2015)

Summary

- Blockade of CB1 block appetite and food intake in animals. CB1 stimulation stimulate appetite in animals and THC administration stimulate appetite in cachexia
- However, in humans epidemiology, cannabis use is associated with lower BMI, less prevalence of Obesity
- Chronic THC treatment inhibits food intake and prevents high fat diet-induced weight gain and adiposity in a mice model of obesity
- The effects of chronic THC treatment are not due to sedation or altered GI transit
- Potentially due to changes in gut microbiota, with increases in "beneficial" bacteria
- But cannabis may also be part of the solution!! By shedding new light on gut-microbial interactions that potential promote healthy metabolism.



Cannabis

1) Cannabis and Addiction
2) Cannabis and Weight
3) Cannabis and Driving

Impact on Driving

- Considerable media attention on this topic
- Driving under influence of Cannabis (DUIC) increase the risk of collision significantly
- Rates of DUIC superior to rates of driving and drinking in some groups (youth)
- DUIC: 75 to 95 deaths in 2012; 4500 collision related injuries (Canada, 2012)

75

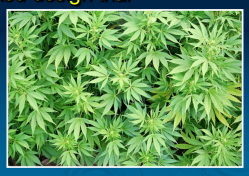
CAMH driving research

- - Impact of cannabis on Driving in young drivers (CIHR, PIs LeFoll, Mann)
- - Impact of cannabis in medical users of cannabis (MOT, PI Brands)
- - Impact of alcohol and cannabis on driving abilities (CIHR, PIs Wickens)
- - Dose Response on driving (Canada Gvt, PI Brands)
- - Impact of Age/Tolerance on driving (PI, Wickens)

76

CAMH driving research

- Purpose: To examine the acute effects of a moderate dose of smoked cannabis (12.5% THC), with or without distraction, on the simulated driving behaviour of young drivers aged 19-25 years
- Study Design: double-blind, 2:1 randomized, placebo-controlled, mixed-design trial



CAMH driving research

- Inclusion criteria:
  - Aged 19-25 years
  - Smoked 1-4 days per week
  - Held a valid Ontario class G or G2 license (held for at least 1 year)
  - Able to provide urine positive for THC at eligibility screening
- Exclusion Criteria
  - Regular user of psychoactive medication
  - Met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for Substance Dependence, has a severe medical or psychiatric condition, family history of schizophrenia, etc.
  - Positive for alcohol on any study day

Procedures

- Study consisted of 5 sessions:
  - Session 1: Eligibility
  - Session 2: Practice Day
    - Driving, cognitive/psychomotor measures, VAS, self-report questionnaires about driving behaviour and personality
  - Session 3: Drug Administration (one 12.5% THC or placebo cannabis cigarette)
    - Ad libitum smoking procedure (max. 10 mins)
    - Pre-drug and post-drug driving tasks, cognitive/psychomotor measures, VAS, vitals and blood samples
  - Session 4: 24 Hours Measures
    - Driving tasks, cognitive/psychomotor measures, VAS, vitals and blood samples
  - Session 5: 48 Hours Measures
    - Driving tasks, cognitive/psychomotor measures, VAS, vitals and blood samples

Sample Characteristics (Mean ± SD)

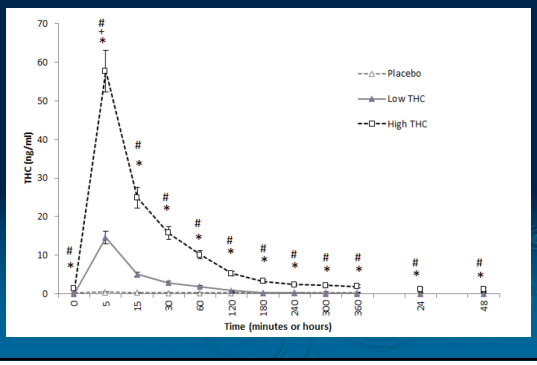
Table 1. Participant characteristics by group (mean (SD) unless noted)

	Placebo n=30	Low THC n=31	High THC n=30	p
Age (years)	21.9 (2.2)	22.2 (1.8)	22.3 (2.0)	n.s.
Sex*				
Female %	**30.0^{a,b}**	**41.9^{b}**	**13.3^{a}**	**0.046**
BMI (kg/m^2)	24.6 (4.3)	23.9 (4.7)	25.4 (4.4)	n.s.
Frequency of cannabis use (days/week)	2.8 (1.1)	2.4 (0.9)	2.6 (0.8)	n.s.
THC concentration at time of driving (+30 min; ng/mL)*	**0.3 (0.6)^{a}**	**2.9 (1.8)^{a}**	**15.4 (8.4)^{b}**	**<0.001**

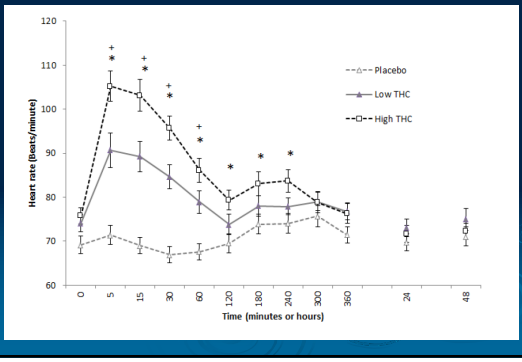
Columns with the same superscript letter are not significantly different at the 0.05 level

From Brands et al, submitted 2018

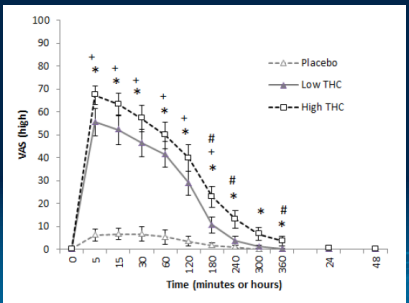
Blood levels of THC



Heart rate



'High' rating



Impact on driving

Table 2. Primary driving outcome measures (presented as change from baseline, post-pre)

	Placebo			Low THC			High THC		
	30min	24hrs	48hrs	30min	24hrs	48hrs	30min	24hrs	48hrs
n	30	29	29	31	31	30	30	30	30
Mean Speed	1.5 (7.4)	2.7 (6.6)	3.1 (6.3)	-0.9 (7.8)	0.3 (5.9)	1.8 (7.1)	-4.8 (10.6)*	1.7 (7.0)	3.5 (8.6)
Mean Speed (DT)	6.6 (10.1)	6.2 (9.4)	4.6 (7.3)	-1.5 (13.7)*	0.3 (10.4)	0.9 (6.1)	-2.1 (10.1)*	3.5 (10.9)	4.1 (8.1)
Lateral Control	0.08 (0.07)	0.01 (0.06)	0.08 (0.08)	0.07 (0.06)	0.001 (0.04)	0.06 (0.06)	0.04 (0.04)	-0.008 (0.05)	0.04 (0.06)
Lateral Control (DT)	0.05 (0.05)	0.1 (0.08)	0.008 (0.04)	0.05 (0.05)	0.1 (0.05)	0.003 (0.05)	0.06 (0.05)	0.1 (0.04)	0.02 (0.04)

Bold text indicates significant group by time interaction in the split-plot ANOVA; DT=dual task condition; Mean speed in km/h; Lateral control in m

*p<0.05, different from placebo

CAMH driving research

- SUMMARY:
- - Illustrate time frame frame of impairement and blood measurement challenges
- - Acute effect noticed on speed primarily in this study
- - No evidence of residual effect the next days

- CHALLENGES OF THIS TYPE OF RESEARCH
- - Require multi-disciplinary teams
- - Require robust infra-structure (driving simulator, negative pressure room, Research pharmacy..)
- -Access to Placebo Cannabis (Import from NIDA Drug supply program (DEA, HC, Exemption, permit…)

85

Conclusions

- Cannabis is addictive
- Cannabis Use Disorders prevention: LRCUG
- CUD Treatment: Effective behavioral treatments are available. Currently no approved pharmacotherapies for the treatment of CUD.
- Cannabinoid drugs may have therapeutic properties: THC/CBD mixture for CUD treatment ? FAAH Blocker promising alternative. Cannabinoid blockers (neutral antagonist, allosteric modulators, still experimental)
- Cannabinoid drugs (THC and/or CBD) may have utility for opioid crisis: possible opioid sparing or blocking of craving by CBD (This is still experimental)

Conclusions

- Little know yet on Medical utility of cannabis (multiple areas of interest: pain, sleep, anxiety, addiction….)
- Evidence needs to be built. Timing is perfect
- Challenges: require some significant infrastructure, Access to drug supply, Access to placebo
- As always in research, multi-disciplinary team with the right expertise will be more appropriate to tackle this issue
- We should approach the area with an open mind. We may find the opposite of what we expect. Let's built the evidence to determine the benefit/risk of cannabis for various conditions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