Medical Marijuana:

Perspective from a Proponent

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Neurologist

Athens, OH

Disclosures

- **I have no ownership of, investment interest in, or compensation agreement with any medical marijuana entity**

- **Certificate To Recommend Medical Marijuana since April 2019 (70+ patients).**

Why take Medical Marijuana?

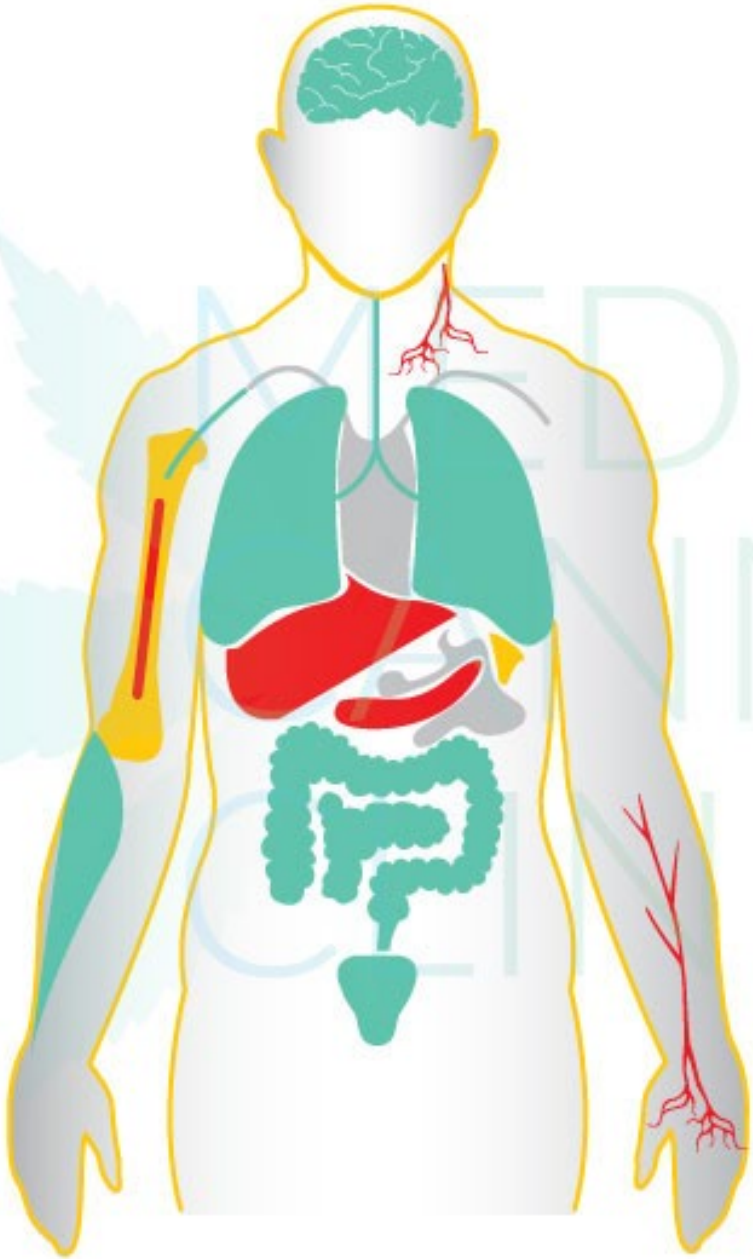
1. **Is it safe?**

2. **Does it work?**

Medical marijuana contains >113 cannabinoids

- **THC** (Tetrahydrocannabinol)
- **CBD** (Cannabidiol)
- CBN (Cannabinol)
- THCA (Tetrahydrocannabinolic acid)
- CBDA (Cannabidiolic Acid)
- CBG (Cannabigerol)
- CBC (Cannabichromene)
- CBL (Cannabicyclol)
- CBV (Cannabivarin)
- THCV (Tetrahydrocannabivarin)
- CBDV (Cannabidivarin)
- CBCV (Cannabichromevarin)
- CBGV (Cannabigerovarin)
- CBGM (Cannabigerol Monomethyl Ether)
- CBE (Cannabielsoin)
- CBT (Cannabicitran) . . .

Cannabinoid Receptors are Ubiquitous



MEDICAL CANNABIS CLINIC AUSTRALIA

CB1 present:

1. central nervous system (braine & spine)
2. lungs
3. vascular system
4. muscles
5. gastrointestinal tract
6. reproductive organs

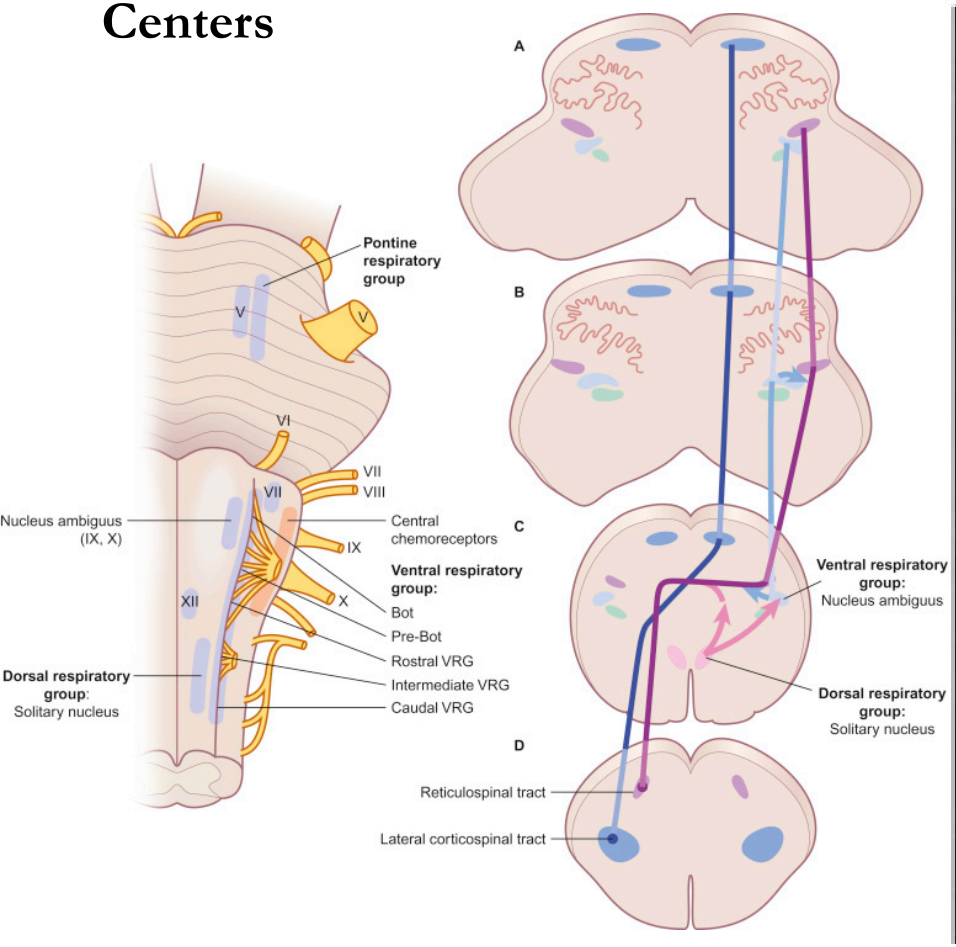
CB2 present:

1. spleen
2. bones
3. skin

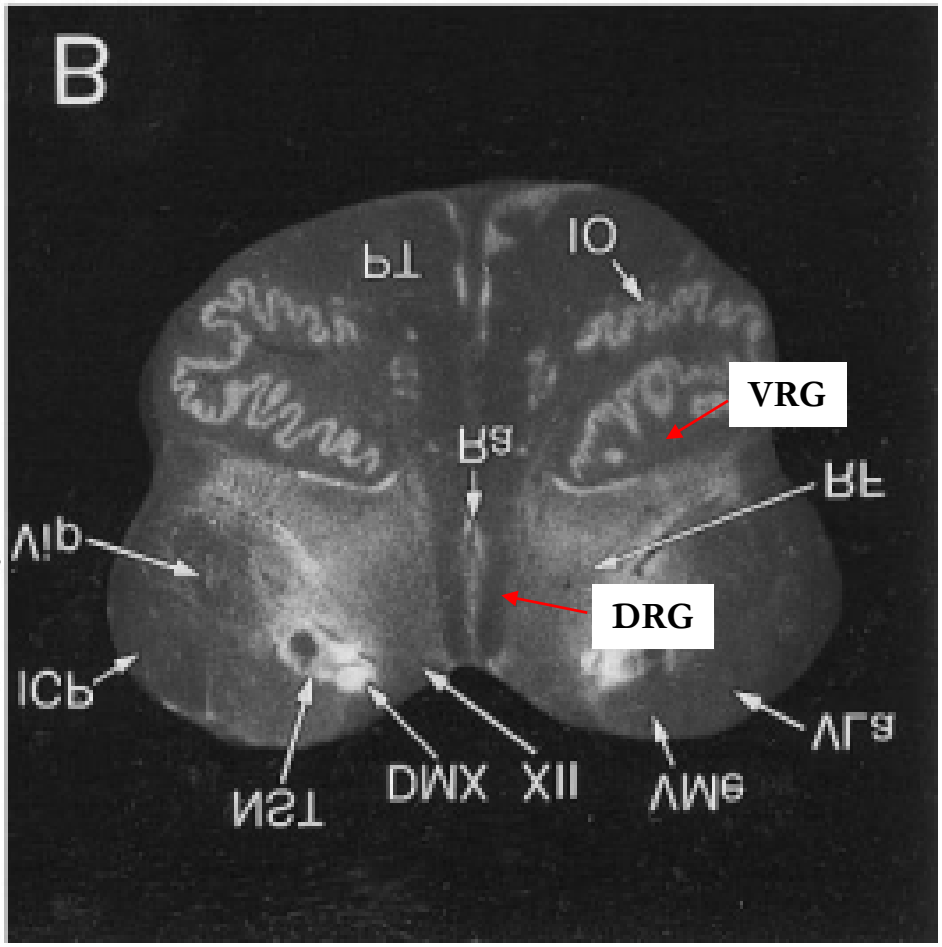
CB1 + CB2 present:

1. immune system
2. liver
3. bone marrow
4. pancreas

Brainstem Respiratory Centers



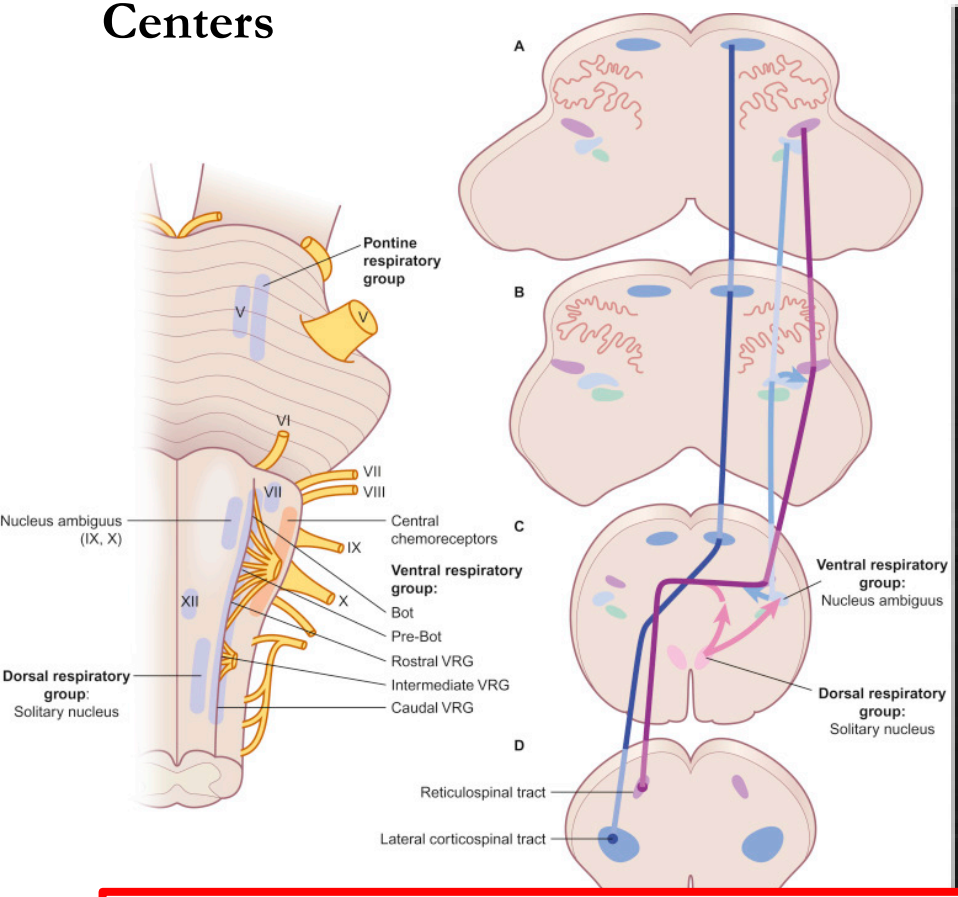
Adult upper medulla



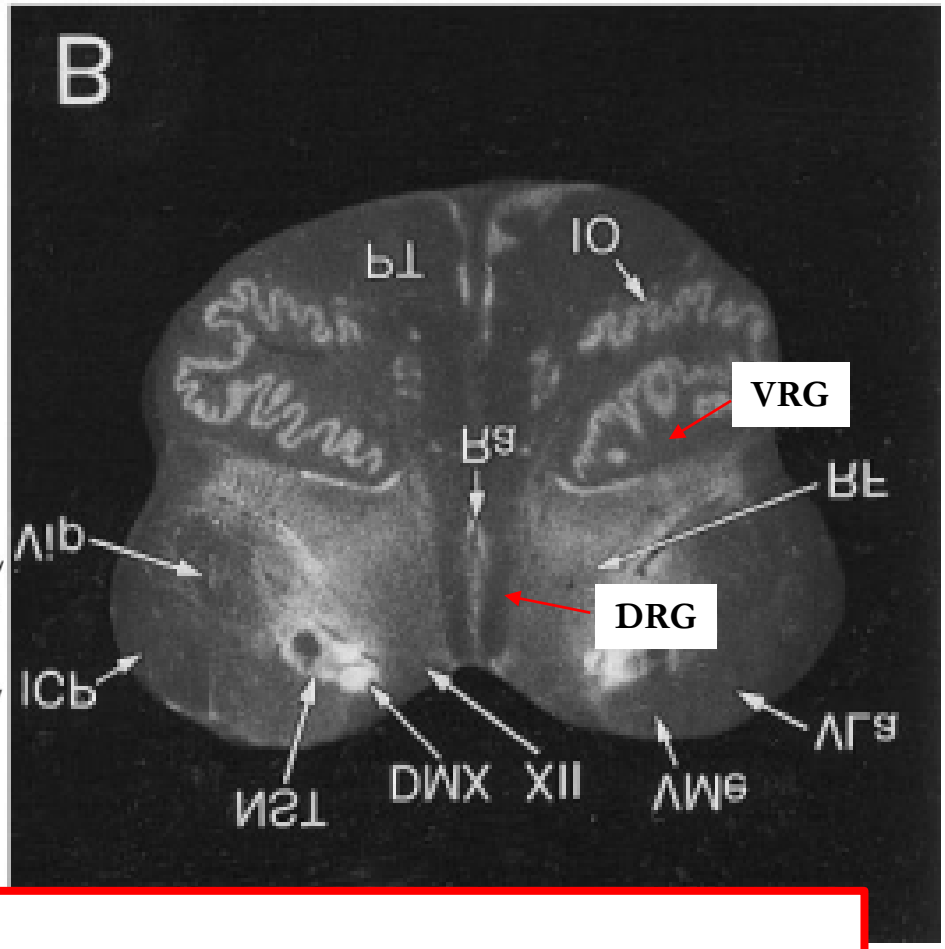
*** There are NO cannabinoid receptors in the brainstem respiratory centers**

Neuroscience Vol. 77, No. 2, pp. 299–318, 1997

Brainstem Respiratory Centers



Adult upper medulla

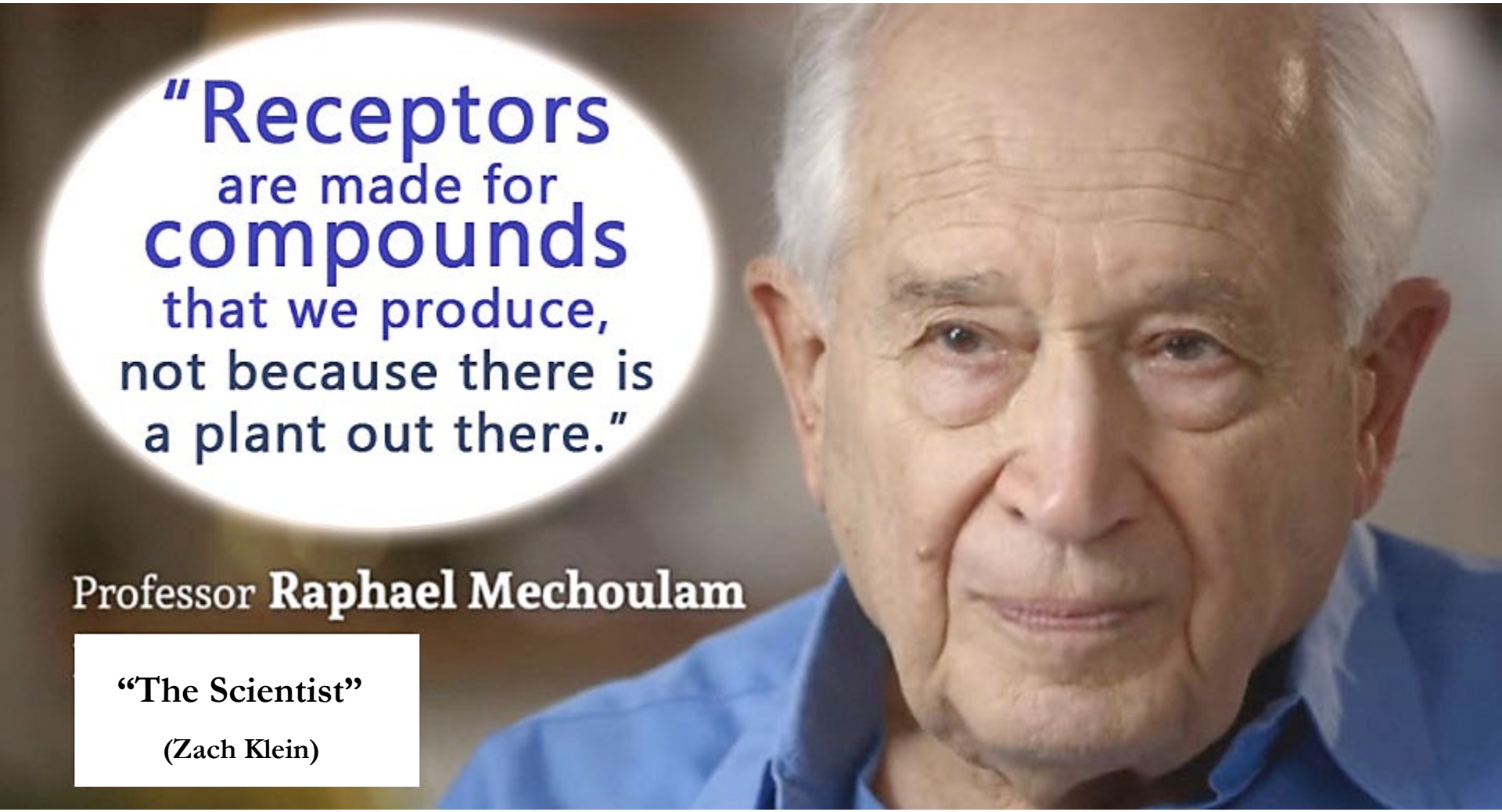


The calculated lethal dose is extremely high:

→ 3 lbs smoked **→ 46 lbs eaten**

Neuroscience Vol. 77, No. 2, pp. 299–318, 1997

Why do Cannabinoid Receptors exist in the human body?



Why do Cannabinoid Receptors exist in the human body?

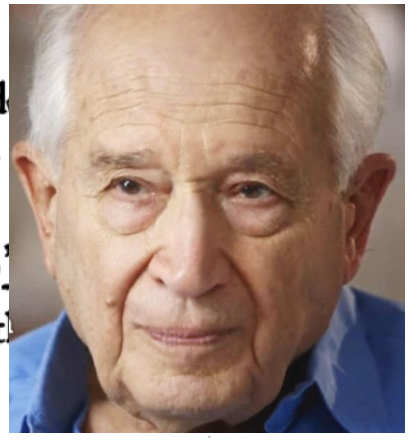
- Hypothesis: CB receptors evolved to respond to cannabinoid ligands that are produced within the body itself.
- Led to a search for **Endocannabinoids**

Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor

William A. Devane,*† Lumir Hanuš, Aviva Breuer, Roger G. Pertwee, Lesley A. Stevenson, Graeme Griffin, Dan Gibson, Asher Mandelbaum, Alexander Etinger, Raphael Mechoulam†

Arachidonylethanolamide, an arachidonic acid derivative in porcine brain, was identified in a screen for endogenous ligands for the cannabinoid receptor. The structure of this compound, which has been named "anandamide," was determined by mass spectrometry and nuclear magnetic resonance spectroscopy and was confirmed by synthesis. Anandamide inhibited the specific binding of a radiolabeled cannabinoid probe to synaptosomal membranes in a manner typical of competitive ligands and produced a concentration-dependent inhibition of the electrically evoked twitch response of the mouse vas deferens, a characteristic effect of psychotropic cannabinoids. These properties suggest that anandamide may function as a natural ligand for the cannabinoid receptor.

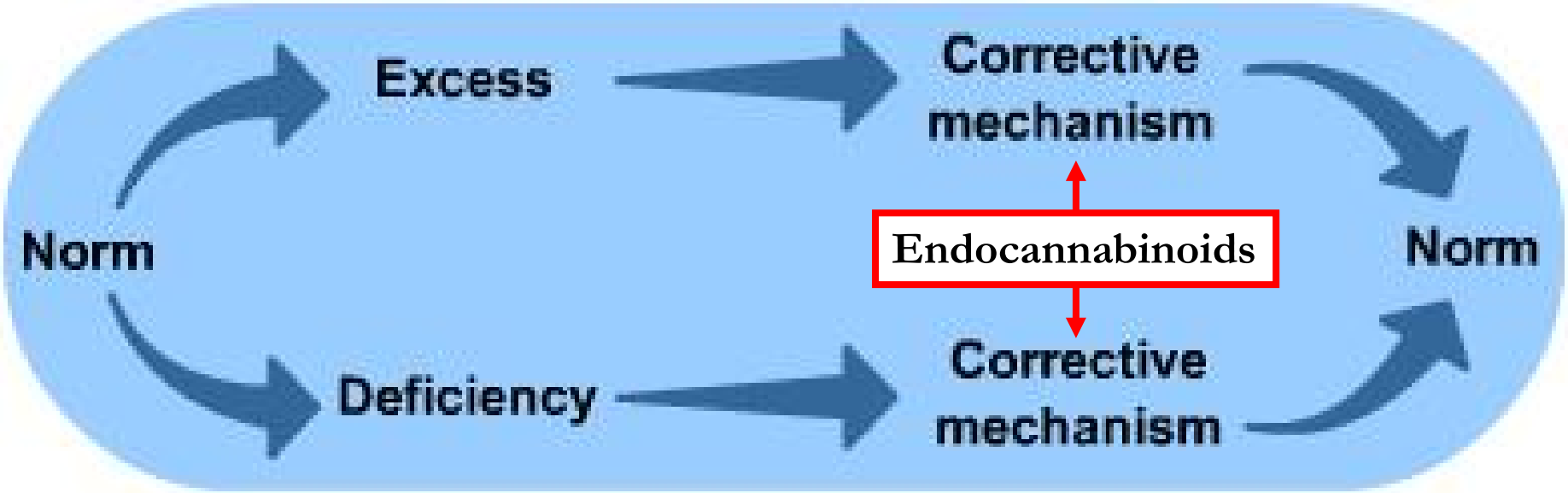
The psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC) (*1*), binds to a specific G protein–coupled receptor in the brain (*2*). Sequence information on the cannabinoid receptor is available from cloned rat (*3*) and human (*4*) genes, but thus far it has not provid the protein's physiological abundance and anatomical the receptor in the brain (*5*), the behavioral effects of Δ^9- consistent with roles in t



Six Endocannabinoids have been identified so far:

1. **Arachidonoyleethanolamine (Anandamide)**
2. **2-Arachidonoylglycerol (2-AG)**
3. **2-Arachidonyl glyceryl ether (noladin ether)**
4. **N-arachidonoyl dopamine (NADA)**
5. **Virodhamine (OAE)**
6. **Lysophosphatidylinositol (LPI)**

Endocannabinoids maintain Homeostasis



***Produced on demand by different cells (e.g. neurons), then rapidly deactivated.**

The Endocannabinoid System

Involved in recovery and repair after insults to the body.

→ Infection/inflammation

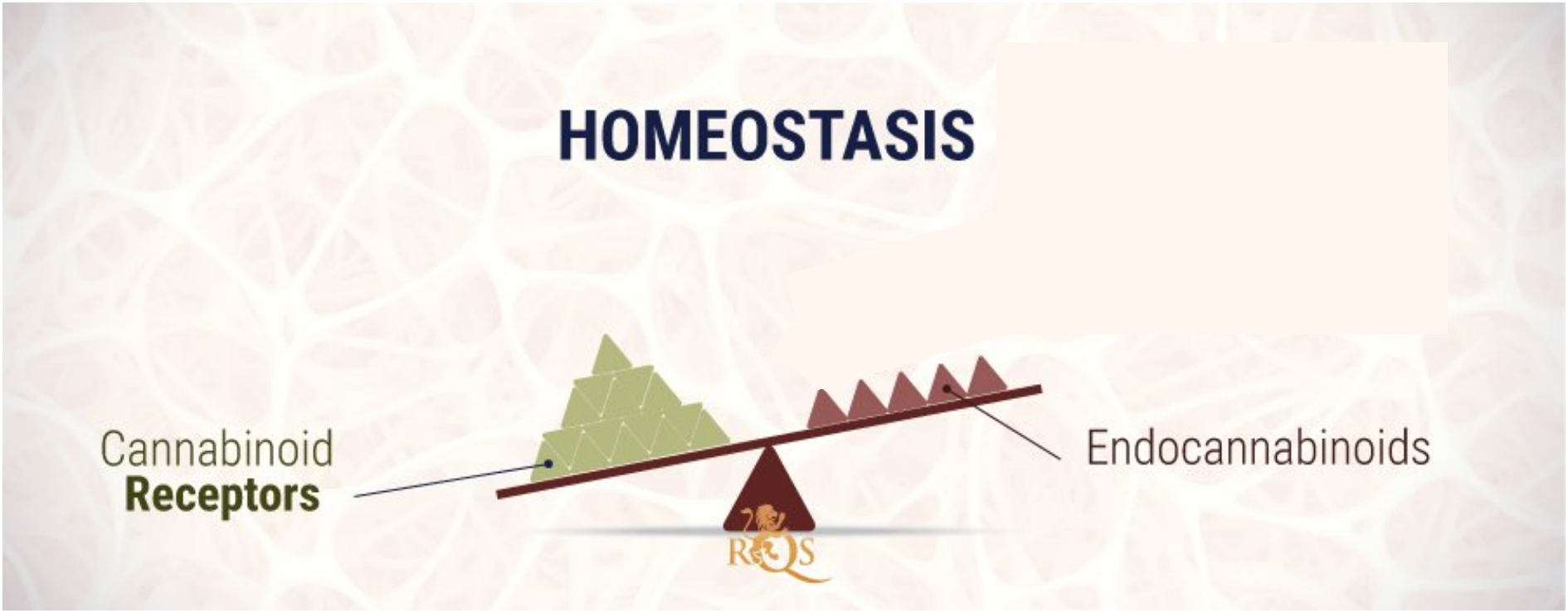
→ Cancer

→ Trauma (physical, emotional)

→ Hypoxia

→ Toxins

What if the body does not produce sufficient Endocannabinoids ?



What if the body does not produce sufficient

Endocannabinoids ? → loss of homeostasis → DISEASE

Cannabis and Cannabinoid Research
Volume 1.1, 2016
DOI: 10.1089/can.2016.0009

Cannabis and Cannabinoid Research

Mary Ann Liebert, Inc. publishers

REVIEW Open Access

Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes

Ethan B. Russo* (child neurologist)

Hypothesis:

- Disease develops in people whose Endocannabinoid levels are lower than normal, and are unable to maintain homeostasis.

Endocannabinoid Deficiency in Migraine

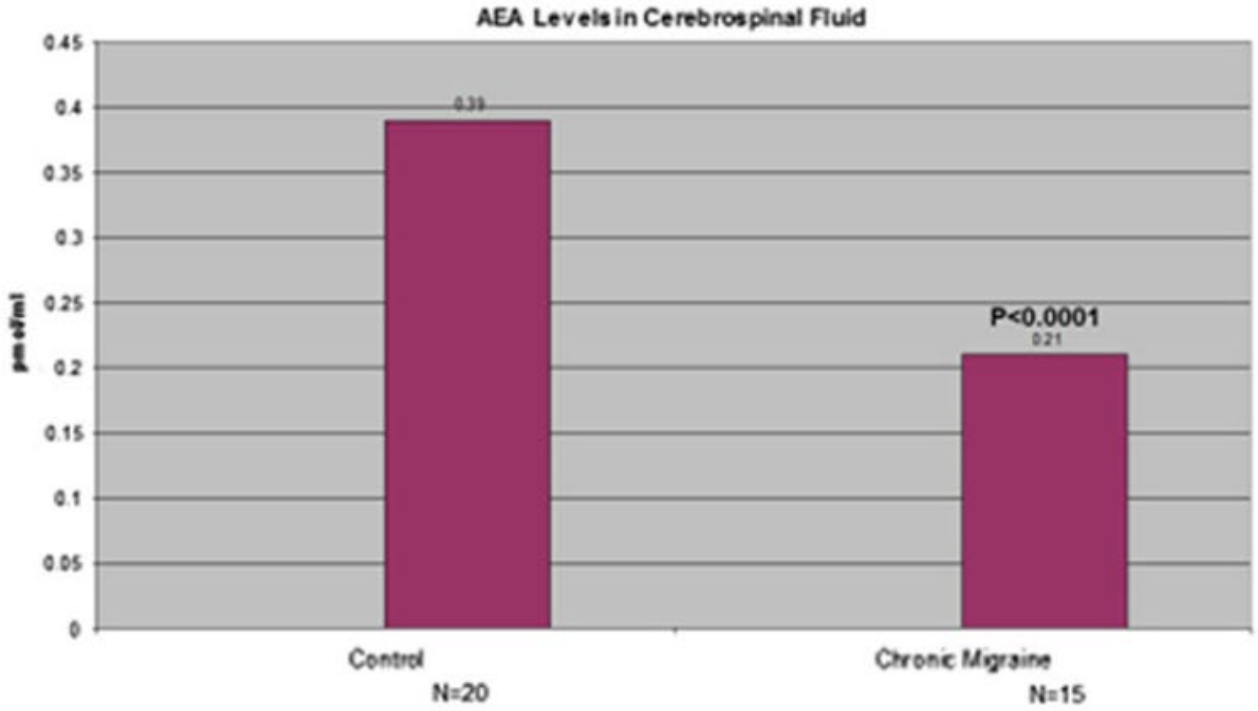
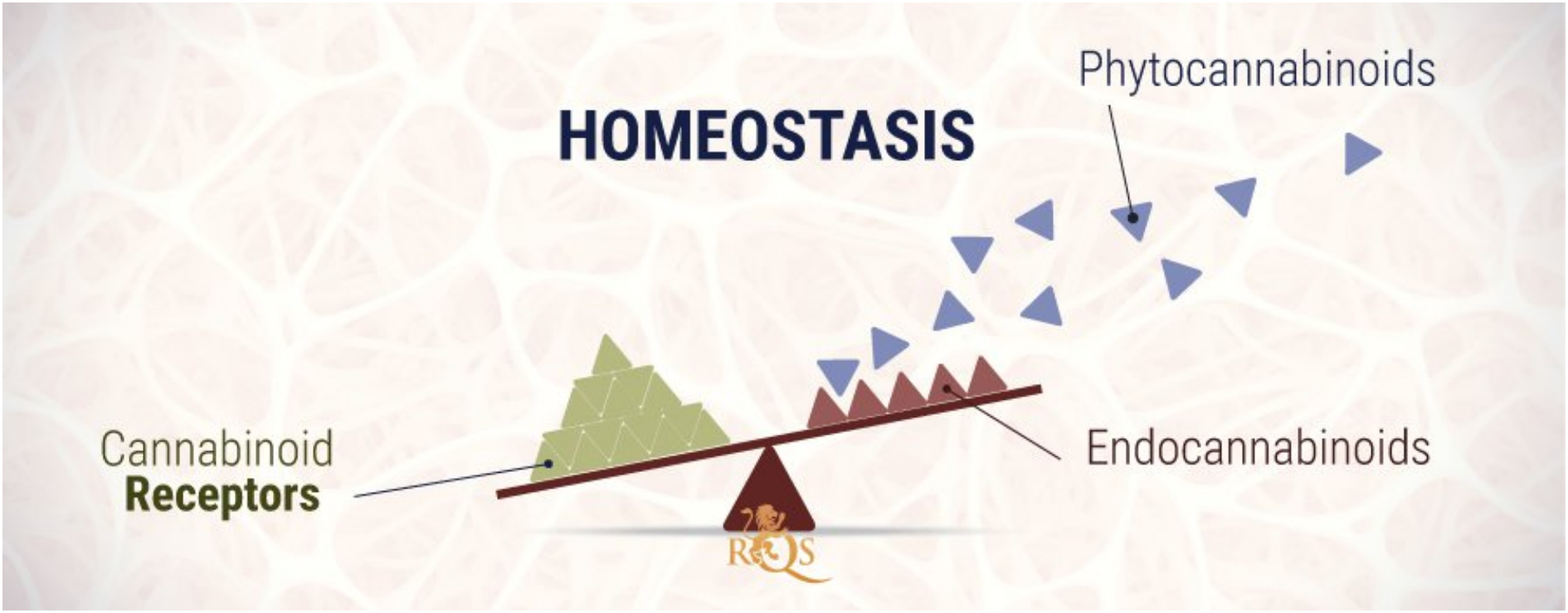


FIG. 2. Anandamide levels in cerebrospinal fluid of chronic migraine patients versus controls, adapted from data obtained from Sarchielli et al.[51]

The phytocannabinoids in medical marijuana replace the deficient endocannabinoids and restore homeostasis.



JAMA Psychiatry | Original Investigation

Association of Combined Patterns of Tobacco and Cannabis Use in Adolescence With Psychotic Experiences

Hannah J. Jones, PhD; Suzanne H. Gage, PhD; Jon Heron, PhD; Matthew Hickman, PhD; Glyn Lewis, PhD; Marcus R. Munafò, PhD; Stanley Zammit, PhD

Table 2. Associations Between Cigarette and/or Cannabis Use and Psychotic Experiences at Age 18 Years

	Definite Psychotic Experiences (n = 3328)			
	Unadjusted		Adjusted	
Variable	OR (95% CI)[a]	*P* Value[b]	OR (95% CI)[a,c]	*P* Value[b]
Early-onset				
Cigarette-only	3.03 (1.13-8.14)	<.001	1.78 (0.54-5.88)	<.001
Cannabis	3.79 (1.73-8.31)		3.70 (1.66-8.25)	
Late-onset				
Cigarette-only	0.84 (0.31-2.31)		0.73 (0.27-1.98)	
Cannabis	3.05 (1.69-5.53)		2.97 (1.63-5.40)	

Abbreviation: OR, odds ratio.

[a] Compared with nonusers class.

[b] The omnibus *P* value for associations between cigarette and/or cannabis use classes and psychotic experiences at age 18 years.

[c] Adjusted for sex, maternal education, emotional and behavioral problems (Strengths and Difficulties Questionnaire score at age 9 years), and maternal cigarette smoking during pregnancy.

JAMA Psychiatry. 2018;75(3):240-246.

Question:

What if a healthy person who does not have diabetes mellitus takes insulin?

→ hypoglycemia, organ damage, death

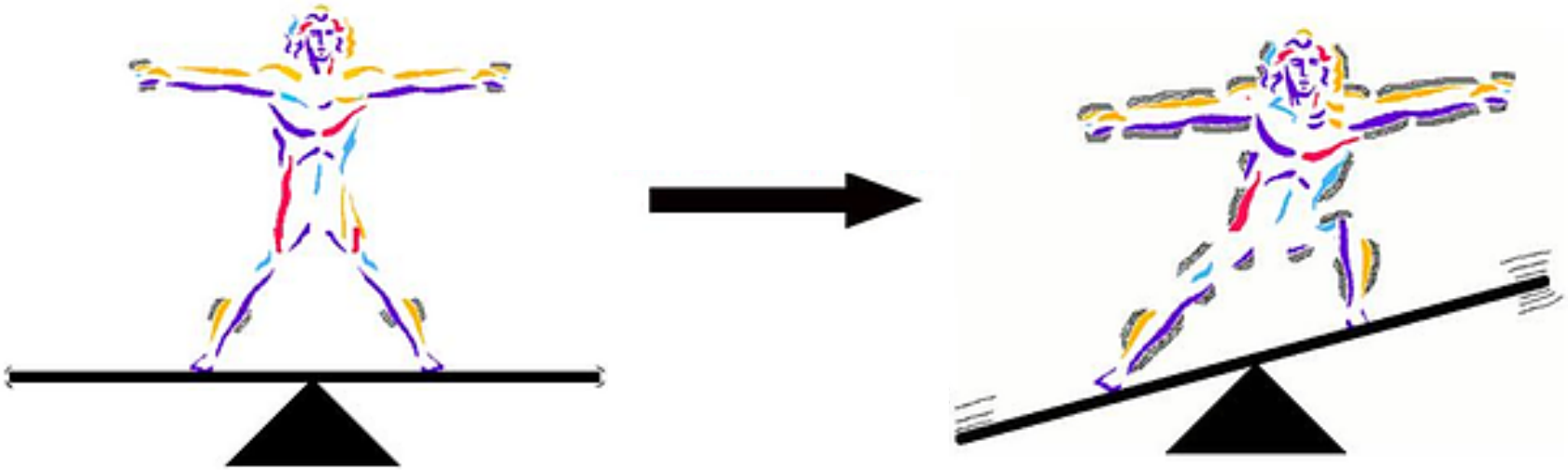
What if a healthy person (without endocannabinoid deficiency) takes marijuana?

What if a healthy person (without endocannabinoid deficiency) takes marijuana?

→ overstimulate CB receptors, downregulate expression

→ disrupts endocannabinoid balance

→ cognitive deficits, psychosis



May be inaccurate to extrapolate the effects of recreational marijuana in healthy subjects to medical marijuana in patients with disease.

Why not just use CBD

and avoid the potential

side effects of THC in

medical marijuana?

The Entourage Effect

- **THC and CBD each exert medicinal effects individually.**

- **When taken together, however, THC and CBD act synergistically:**

  → **Greater efficacy**

  → **Reduced side effects**

Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

Jeremy R. Johnson, MB ChB, Mary Burnell-Nugent, MB BChir, Dominique Lossignol, MB ChB, MRCG, DRCOG, Elena Doina Ganae-Motan, MD, Richard Potts, BSc (Hons), MICR, and Marie T. Fallon, MB ChB, MD, FRCP (E), FRCP (Glasg)

Severn Hospice (J.R.J.), Shrewsbury, Shropshire, and St. Luke's Hospice (M.B.-N.), Turnchapel, Plymouth, United Kingdom; Association Hospitaliere De Brussels (D.L.), Centre des Tumeurs de l'ULB, Brussels, Belgium; Emergency Department (E.D.G.-M.), Hospital "Sf. Ioan cel Nou," Suceava, Romania; GW Pharma Ltd. (R.P.), Ely, Cambridgeshire; and Edinburgh Cancer Research Centre (M.T.F.), University of Edinburgh, Edinburgh, United Kingdom

60 pts = THC+CBD (1:1 ratio)

58 pts = THC only

59 pts = Placebo

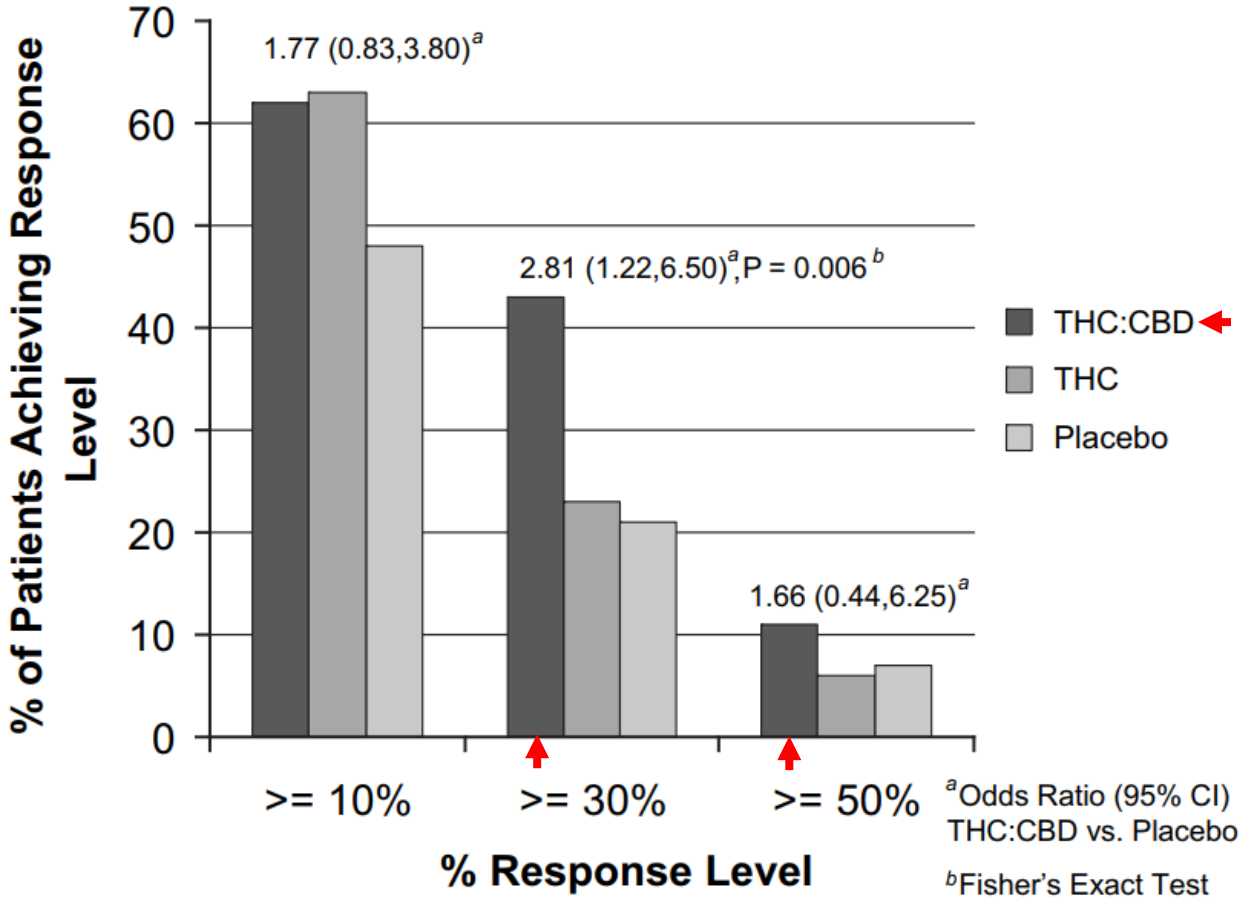


Fig. 3. Pain 0–10 Numerical Rating Scale scores: responder analysis (ITT analysis). [a]Odds ratio (95% CI) THC:CBD vs. placebo; [b]Fisher's exact test.

Systems/Circuits

Acetaminophen Relieves Inflammatory Pain through CB_1 Cannabinoid Receptors in the Rostral Ventromedial Medulla

Pascal P. Klinger-Gratz,[1]* William T. Ralvenius,[1]* Elena Neumann,[1] Ako Kato,[1] Rita Nyilas,[2] Zsolt Lele,[2] István Katona,[2] and Hanns Ulrich Zeilhofer[1,3]

[1]Institute of Pharmacology and Toxicology, University of Zurich, CH-8057 Zurich, Switzerland, [2]Institute of Experimental Medicine, Hungarian Academy of Sciences, H-1083 Budapest, Hungary, and [3]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich, CH-8093 Zürich, Switzerland

Acetaminophen (paracetamol) is a widely used analgesic and antipyretic drug with only incompletely understood mechanisms of action. Previous work, using models of acute nociceptive pain, indicated that analgesia by acetaminophen involves an indirect activation of CB_1 receptors by the acetaminophen metabolite and endocannabinoid reuptake inhibitor AM 404. However, the contribution of the cannabinoid system to antihyperalgesia against inflammatory pain, the main indication of acetaminophen, and the precise site of the relevant CB_1 receptors have remained elusive. Here, we analyzed acetaminophen analgesia in mice of either sex with inflammatory pain and found that acetaminophen exerted a dose-dependent antihyperalgesic action, which was mimicked by intrathecally injected AM 404. Both compounds lost their antihyperalgesic activity in $CB_1^{-/-}$ mice, confirming the involvement of the cannabinoid system. Consistent with a mechanism downstream of proinflammatory prostaglandin formation, acetaminophen also reversed hyperalgesia induced by intrathecal prostaglandin E_2. To distinguish between a peripheral/spinal and a supraspinal action, we administered acetaminophen and AM 404 to *hoxB8*-$CB_1^{-/-}$ mice, which lack CB_1 receptors from the peripheral nervous system and the spinal cord. These mice exhibited unchanged antihyperalgesia indicating a supraspinal site of action. Accordingly, local injection of the CB_1 receptor antagonist rimonabant into the rostral ventromedial medulla blocked acetaminophen-induced antihyperalgesia, while local rostral ventromedial medulla injection of AM 404 reduced hyperalgesia in wild-type mice but not in $CB_1^{-/-}$ mice. Our results indicate that the cannabinoid system contributes not only to acetaminophen analgesia against acute pain but also against inflammatory pain, and suggest that the relevant CB_1 receptors reside in the rostral ventromedial medulla.

Key words: acetaminophen; AM 404; analgesia; inflammation; N-arachidonoylphenolamin; paracetamol

International Journal of Obstetric Anesthesia (2015) 24, 210–216
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2015.03.006

ORIGINAL ARTICLE

ELSEVIER
www.obstetanesthesia.com

Scheduled acetaminophen with as-needed opioids compared to as-needed acetaminophen plus opioids for post-cesarean pain management

A.R. Valentine,[a] B. Carvalho,[b] T.A. Lazo,[b] E.T. Riley[b]
[a]*Stanford University School of Medicine, Stanford, CA, USA*
[b]*Department of Anesthesia, Stanford University Medical Center, Stanford, CA, USA*

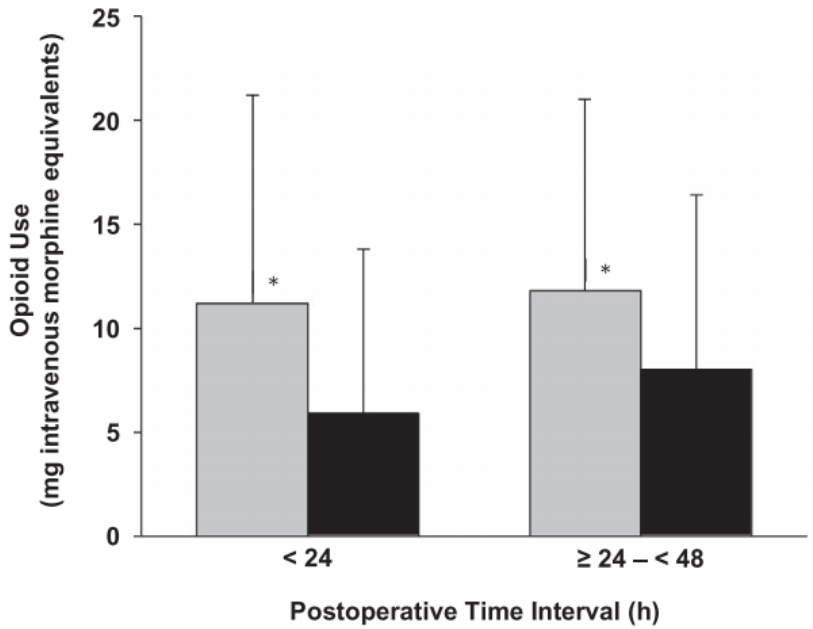


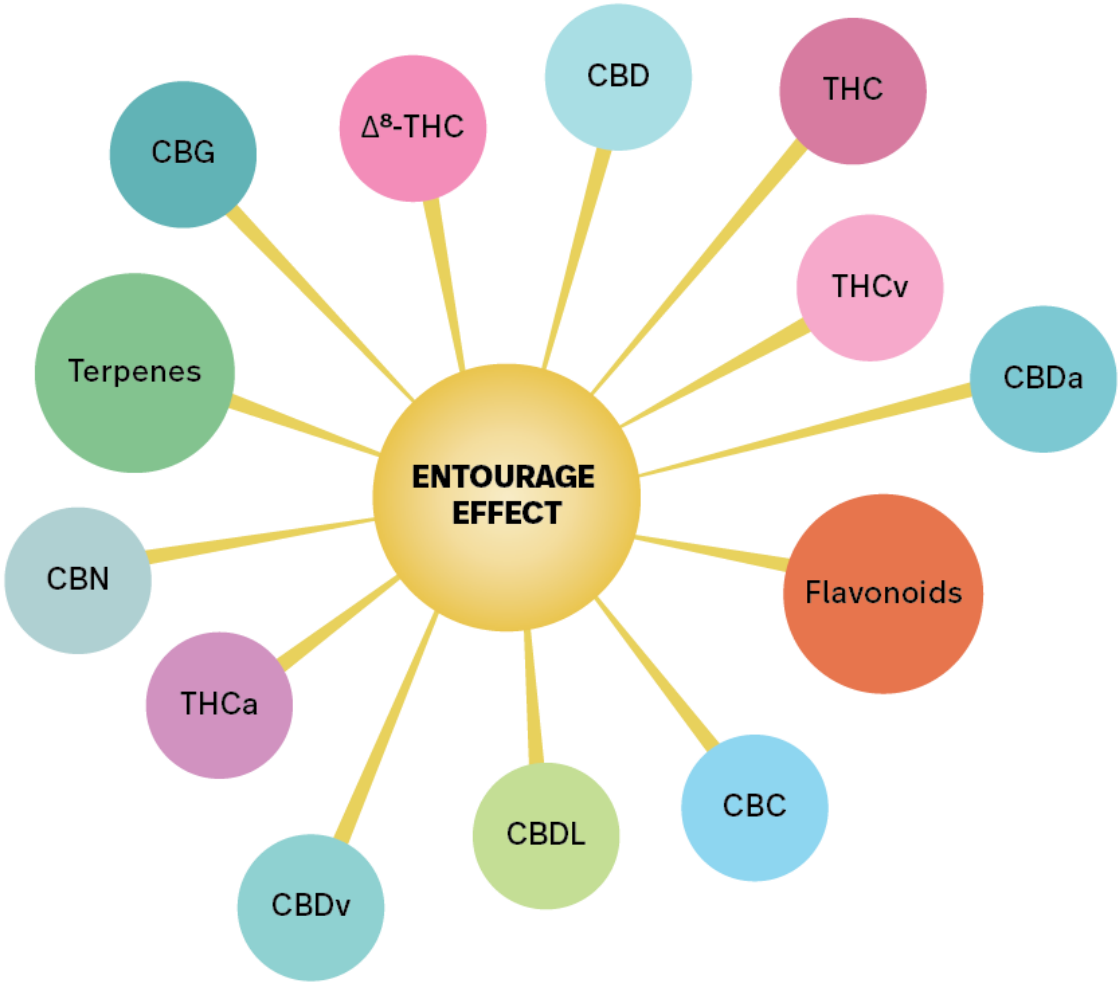
Fig. 2 Opioid use in mg intravenous morphine equivalents after cesarean delivery in 24-h increments by group. As-Needed Group are grey bars; Scheduled Group are black bars. Data are mean ± SD, *significant difference between groups ($P \leqslant 0.001$).

Acetaminophen

650mg Q6hr x 48 hr

The Entourage Effect is further magnified by:

- All the other 110+ cannabinoids
- Terpenoids
- Flavonoids



The Endocannabinoid System

Involved in recovery and repair after insults to the body.

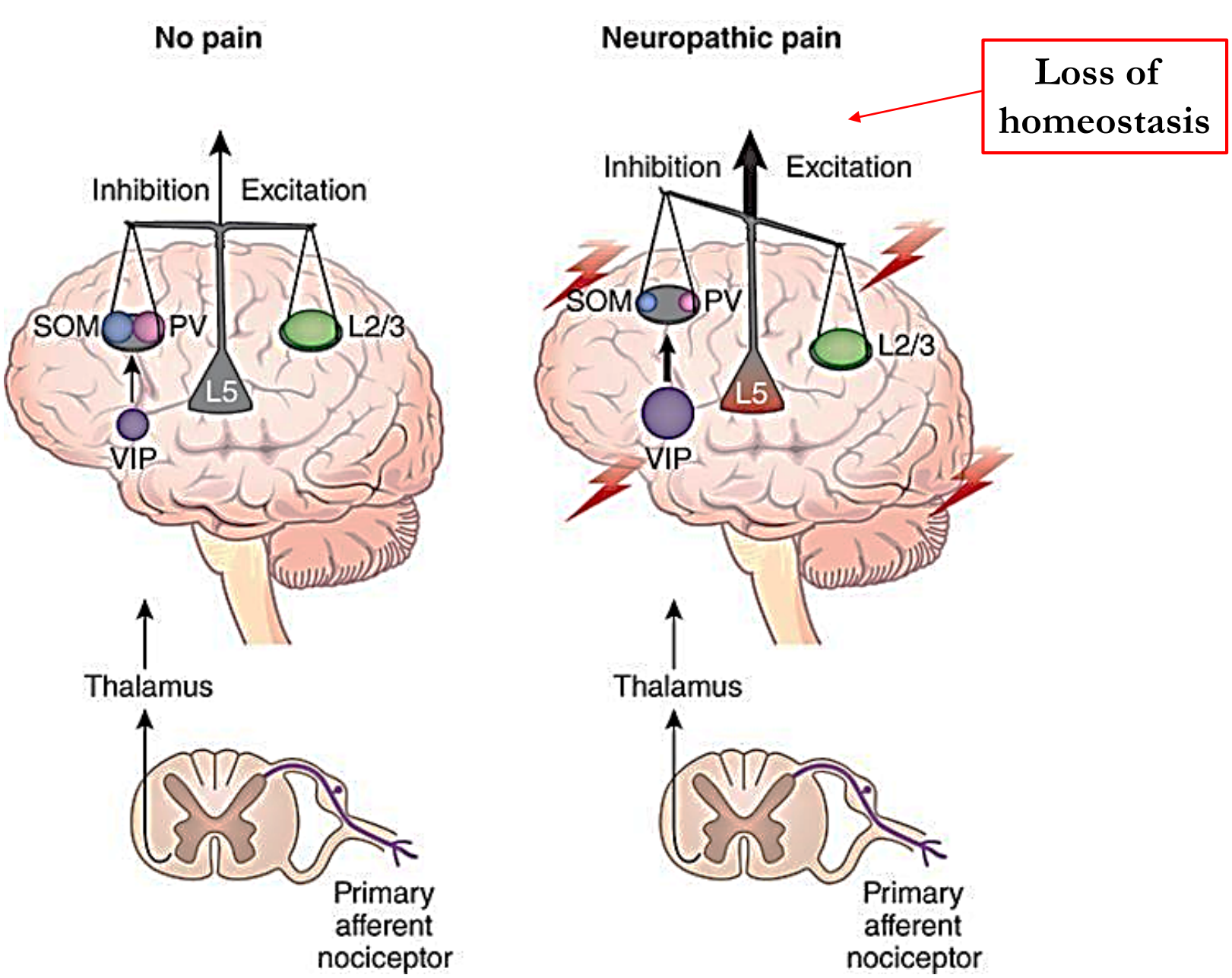
→ Infection/inflammation

→ Cancer

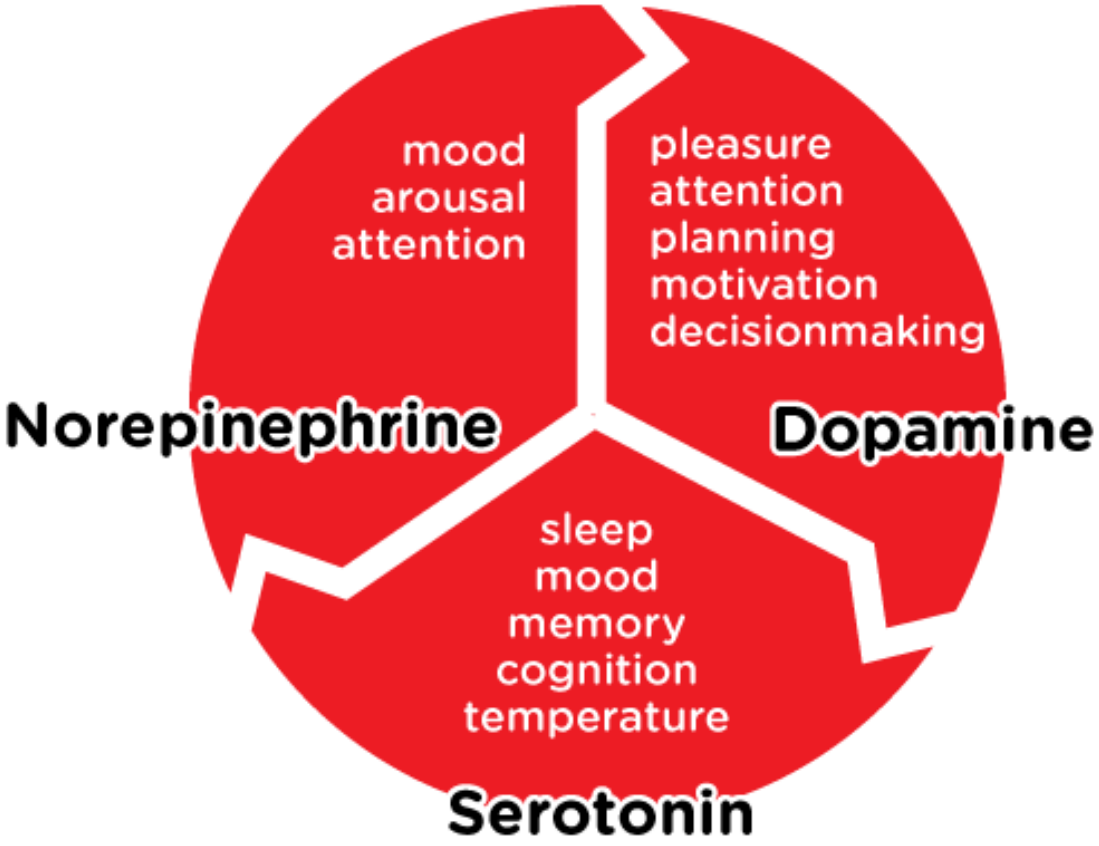
→ Trauma (physical, emotional)

→ Hypoxia

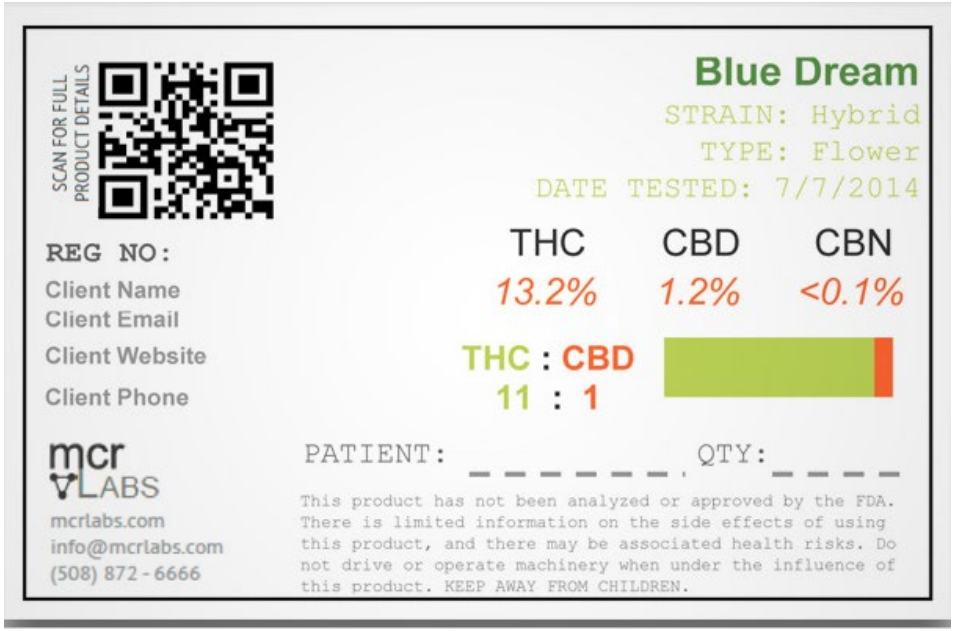
→ Toxins

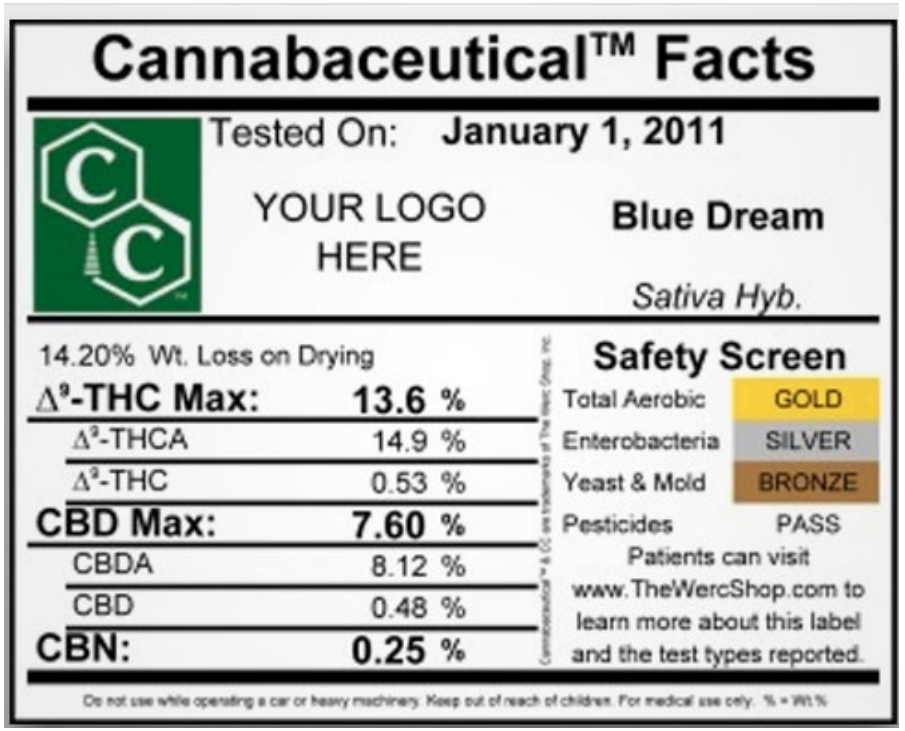

No pain
Neuropathic pain
Loss of homeostasis
Inhibition
Excitation
SOM
PV
L2/3
L5
VIP
Thalamus
Primary afferent nociceptor
Inhibition
Excitation
SOM
PV
L2/3
L5
VIP
Thalamus
Primary afferent nociceptor

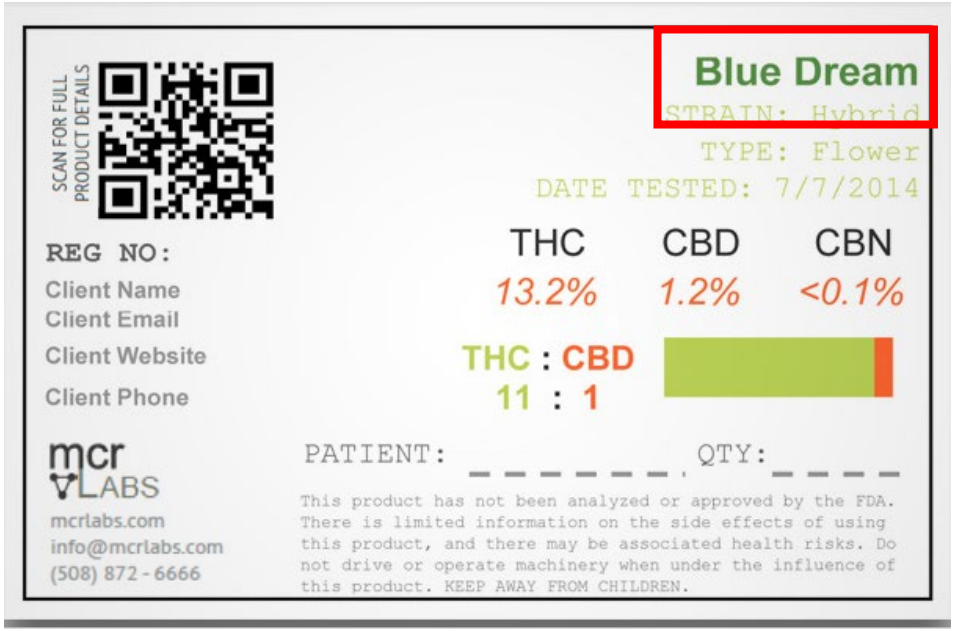
Homeostasis and Mood

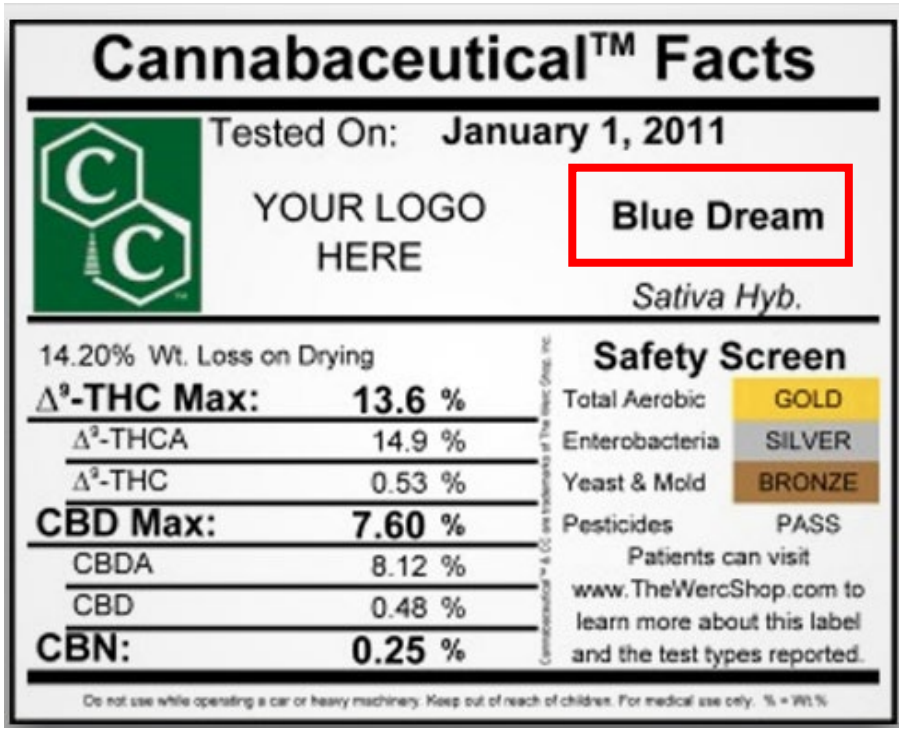


"A chemical imbalance in the brain"


SCAN FOR FULL PRODUCT DETAILS
Blue Dream
STRAIN: Hybrid
TYPE: Flower
DATE TESTED: 7/7/2014
REG NO:
Client Name
Client Email
Client Website
Client Phone
THC
CBD
CBN
13.2%
1.2%
<0.1%
THC : CBD
11 : 1
mcr LABS
mcrlabs.com
info@mcrlabs.com
(508) 872 - 6666
PATIENT:
QTY:
This product has not been analyzed or approved by the FDA. There is limited information on the side effects of using this product, and there may be associated health risks. Do not drive or operate machinery when under the influence of this product. KEEP AWAY FROM CHILDREN.


Cannabaceutical™ Facts
Tested On: January 1, 2011
YOUR LOGO HERE
Blue Dream
Sativa Hyb.
14.20% Wt. Loss on Drying
Δ⁹-THC Max: 13.6 %
Δ⁹-THCA 14.9 %
Δ⁹-THC 0.53 %
CBD Max: 7.60 %
CBDA 8.12 %
CBD 0.48 %
CBN: 0.25 %
Safety Screen
Total Aerobic GOLD
Enterobacteria SILVER
Yeast & Mold BRONZE
Pesticides PASS
Patients can visit www.TheWercShop.com to learn more about this label and the test types reported.
Do not use while operating a car or heavy machinery. Keep out of reach of children. For medical use only. % = Wt %


SCAN FOR FULL PRODUCT DETAILS
Blue Dream
STRAIN: Hybrid
TYPE: Flower
DATE TESTED: 7/7/2014
REG NO:
Client Name
Client Email
Client Website
Client Phone
THC
CBD
CBN
13.2%
1.2%
<0.1%
THC : CBD
11 : 1
mcr LABS
mcrlabs.com
info@mcrlabs.com
(508) 872 - 6666
PATIENT:
QTY:
This product has not been analyzed or approved by the FDA. There is limited information on the side effects of using this product, and there may be associated health risks. Do not drive or operate machinery when under the influence of this product. KEEP AWAY FROM CHILDREN.


Cannabaceutical™ Facts
Tested On: January 1, 2011
YOUR LOGO HERE
Blue Dream
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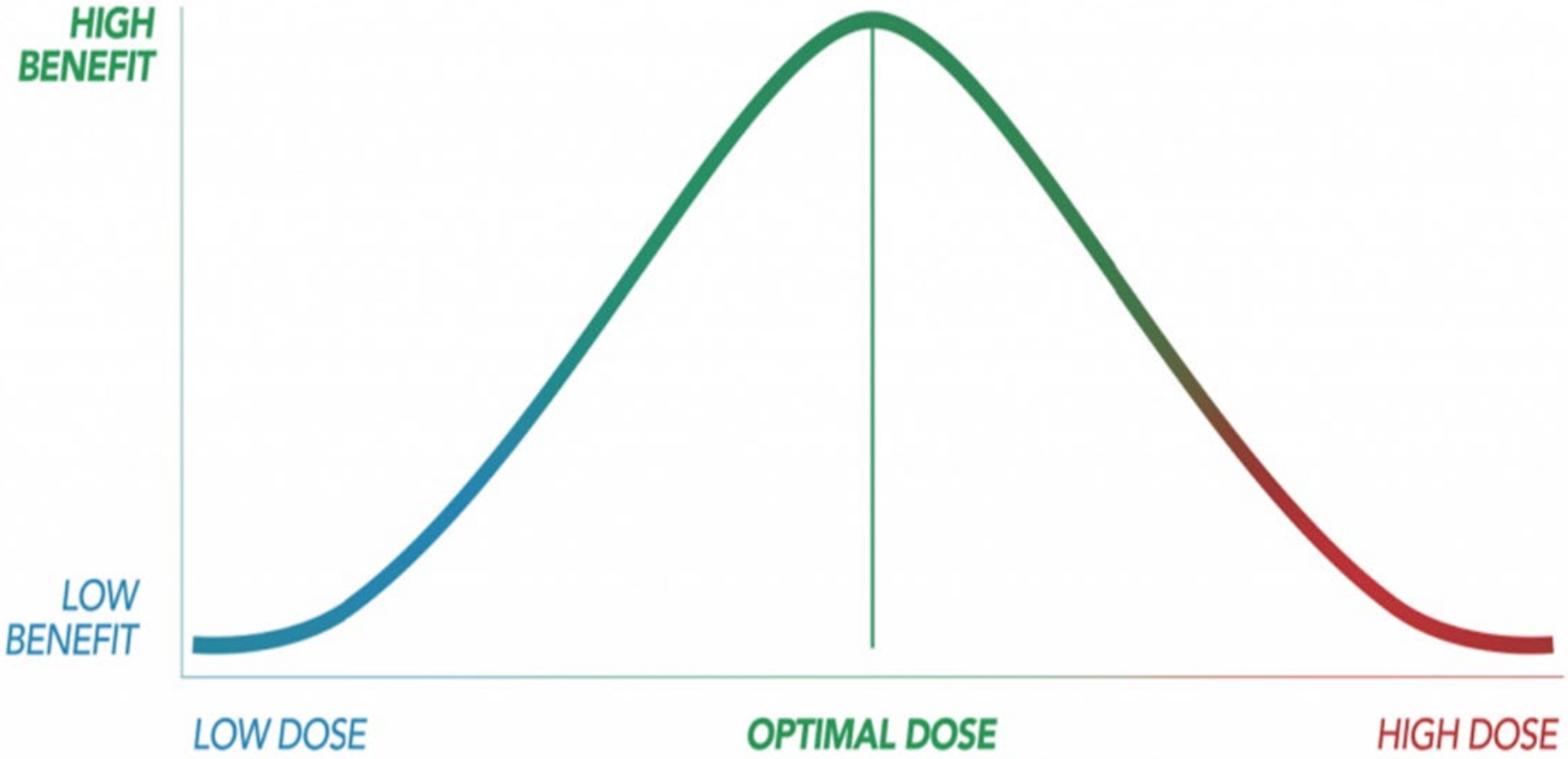
14.20% Wt. Loss on Drying
Δ⁹-THC Max: 13.6 %
Δ⁹-THCA 14.9 %
Δ⁹-THC 0.53 %
CBD Max: 7.60 %
CBDA 8.12 %
CBD 0.48 %
CBN: 0.25 %
Safety Screen
Total Aerobic GOLD
Enterobacteria SILVER
Yeast & Mold BRONZE
Pesticides PASS
Patients can visit www.TheWercShop.com to learn more about this label and the test types reported.
Do not use while operating a car or heavy machinery. Keep out of reach of children. For medical use only. % = Wt %

Marijuana has a Biphasic Dose-Response Curve



Marijuana and Driving

Marijuana causes impairments in:

- **Visual Tracking**
- **Motor coordination**
- **Reaction time**
- **Complex tasks involving divided attention**

Am J Addict. 2009 ; 18(3): 185–193.

Comparison of the Effects of Marijuana and Alcohol on Simulated Driving Performance

BY ALFRED CRANCER, JR., Ph.D.,
JAMES M. DILLE, M.D.,
JACK C. DELAY, M.D.,
JEAN E. WALLACE, M.D.,
& MARTIN D. HAYKIN, M.D.

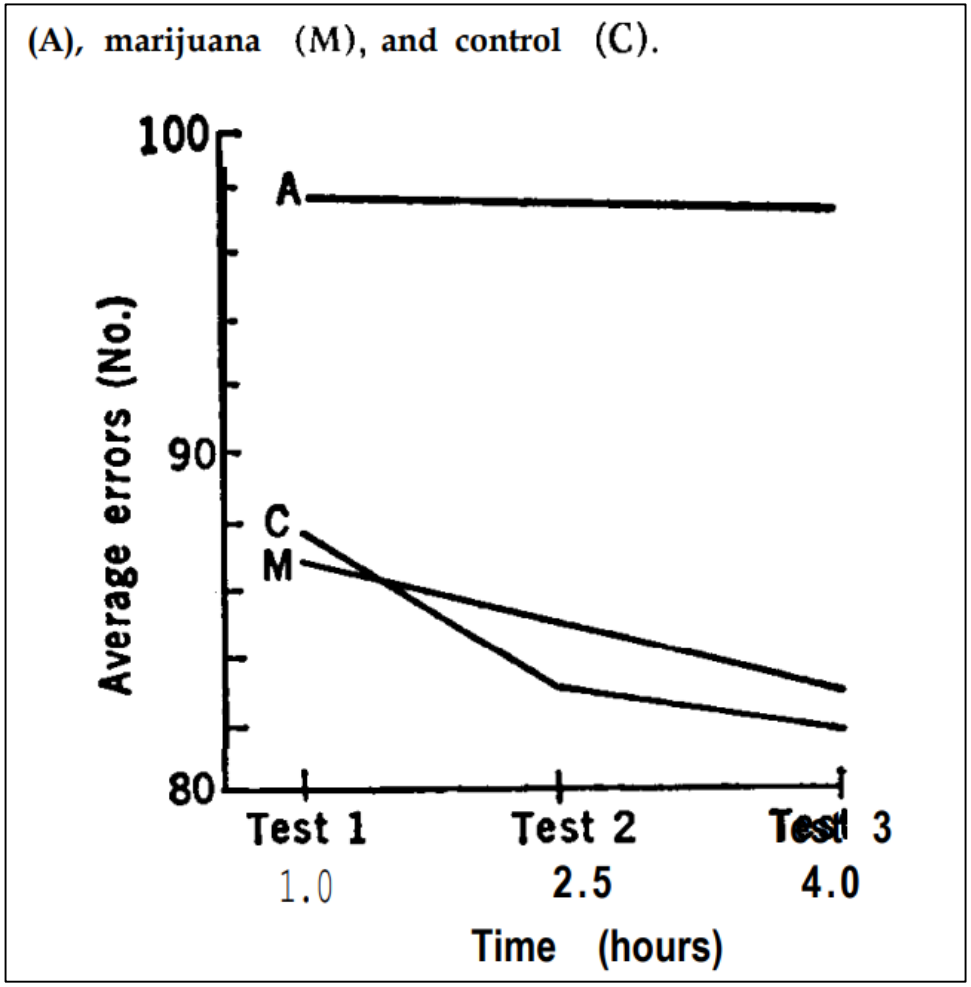
36 subjects

Each did 3 treatment arms:

a. Control

b. 2 marijuana cigarettes

c. 2 alcoholic drinks



Science, vol. 164, May 16, 1969, pp. 851-854.

A significant difference ($P<.01$) was found between the pulse rates before and after the marijuana treatment. Similar results were reported' for both experienced and inexperienced marijuana subjects. We found no significant difference in pulse rates before and after drinking.

Thus, when subjects experienced a social marijuana "high," they accumulated significantly more speedometer errors on the simulator than under control conditions, but there were no significant differences in accelerator, brake, signal, steering, and total errors. The same subjects intoxicated from alcohol accumulated significantly more accelerator, brake, signal, speedometer, and total errors. Furthermore, impairment in simulated driving performance apparently is not a function of increased marijuana dosage or inexperience with the drug.

REFERENCES AND NOTES

Science, vol. 164, May 16, 1969, pp. 851-854.

February 1983
Final Report

DOT HS-806-405

U.S. Department of Transportation
National Highway Traffic Safety Administration

A Simulator Study of the Combined Effects of Alcohol and Marihuana on Driving Behavior—Phase II

A. C. Stein
R. W. Allen
M. L. Cook
R. L. Karl

A full placebo experimental design was employed which included all combinations of 3 marihuana (0, 100, and 200 µg Δ^9 THC/kg body weight) and 2 alcohol (0 and 0.10 percent BAC) levels. Based on a large number of driver performance and behavior variables, alcohol was found to have a pervasive and significant impairing effect. Simulator accidents increased reliably under alcohol, which was accounted for by increased steering and speed control variability. Marihuana effects were minimal, the primary one being speed reduction. This speed reduction, while statistically reliable, was minimal in terms of actual driving behavior and is probably of no practical significance. A significant drug interaction effect was observed in simulator accidents; however, the data do not allow us to identify the impairment mechanism leading to this result.

17. Key Words	18. Distribution Statement
Alcohol Marihuana Driving Behavior Driver Control Alcohol/Marihuana Combined Effects	Document is available to the public through the National Technical Information Service, Springfield, VA 22161

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified		

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THE EFFECT OF CANNABIS COMPARED WITH ALCOHOL ON DRIVING

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3.2.3 Summary of experimental studies

It appears that cannabis use may impair some driving skills (automatic functions such as tracking) at smoked doses as low as 6.25 mg (a third of a joint), but different skills (complex functions that require conscious control) are not impaired until higher doses, and cannabis users tend to compensate effectively for their deficits by driving more carefully. Unexpected events are still difficult to handle under the influence of marijuana, however, and the combination of low-

Drivers on cannabis:

- **overestimated their intoxication level**
- **drove more slowly**
- **had increased follow-on distance**

Am J Addict. 2009 ; 18(3): 185–193.

National Commission on Marijuana and Drug Abuse

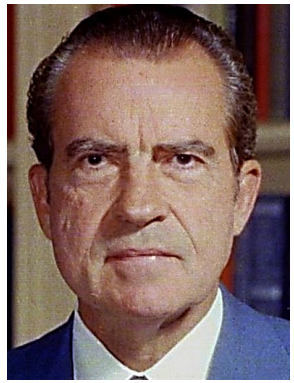
- March 1971 - appointed by Nixon at the direction of Congress
- "Shafer Commission"
- Objective was to determine:
  - the nature and scope of marijuana use
  - the effects of marijuana
  - the relationship of marijuana use to other behavior
- Commissioned 50 studies

National Commission on Marijuana and Drug Abuse

- **March 1972, final report: "Marihuana, A Signal of Misunderstanding"**

- **"There is little proven danger of … harm from the experimental or intermittent use of the natural preparations of cannabis".**

→ ***Recommended Decriminalizing Marijuana***



May 1, 1971

In a televised news conference, President Nixon said:

"As you know, there is a Commission that is supposed to make recommendations to me about this subject . . . however, I have such strong views that I will express them. I am against legalizing marijuana. Even if the Commission does recommend that it be legalized, I will not follow that recommendation . . . I can see no social or moral justification whatever for legalizing marijuana. I think it would be exactly the wrong step. It would simply encourage more and more of our young people to start down the long, dismal road that leads to hard drugs and eventually self-destruction."

Addiction (1998) 93(4), 493–503

RESEARCH REPORT

Marijuana use and treatment outcome among opioid-dependent patients

ALAN J. BUDNEY, WARREN K. BICKEL & LESLIE AMASS

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Abstract

Aims. *Information concerning the association between marijuana use and opioid dependence and its treatment is needed to determine effective clinical guidelines for addressing marijuana use among opioid abusers.* **Setting and participants.** *Marijuana use was assessed in 107 people enrolled in treatment for opioid dependence.* **Design and measurement.** *Univariate comparisons of marijuana users and non-users and multivariate regression analyses were performed to examine associations between marijuana use and socio-demographic, psychosocial, medical and substance-use variables. The relationship between marijuana use and treatment outcome was also explored in a subset of this sample who received treatment that included*

Addiction (1998) 93(4), 493–503

Table 3. *Opioid dependence treatment outcome*

	Marijuana user ($N = 54$)	Non-user ($N = 25$)
Retention* (% of wks completed)	65% (32)	60% (33)
Opiate abstinence (no. of continuous wks)	8.4 (6.5)	8.5 (7.2)
Other drug use (% positive urine specimens)		
Benzodiazepines	32%	40%
Cocaine	13%	14%
ASI composite change scores* (intake—12-month follow-up)		
Medical	−0.07 (0.45)	0.09 (0.50)
Employment	0.05 (0.27)	0.06 (0.35)
Legal	0.03 (0.30)	0.15 (0.22)
Alcohol	0.05 (0.29)	0.10 (0.16)
Drug	0.24 (0.16)	0.20 (0.18)
Family–social	0.11 (0.27)	0.21 (0.26)
Psychiatric	−0.01 (0.30)	0.04 (0.24)

Includes only participants who received buprenorphine and behavioral treatment. Excludes participants who dropped out during the first 2 weeks of treatment.

*mean (standard deviation); **raw change scores are presented to preserve clarity. Only those who completed both ASI assessments are included ($n = 53$). ANCOVA analyses revealed no significant group × time interaction effects across subscales.

Retrospective

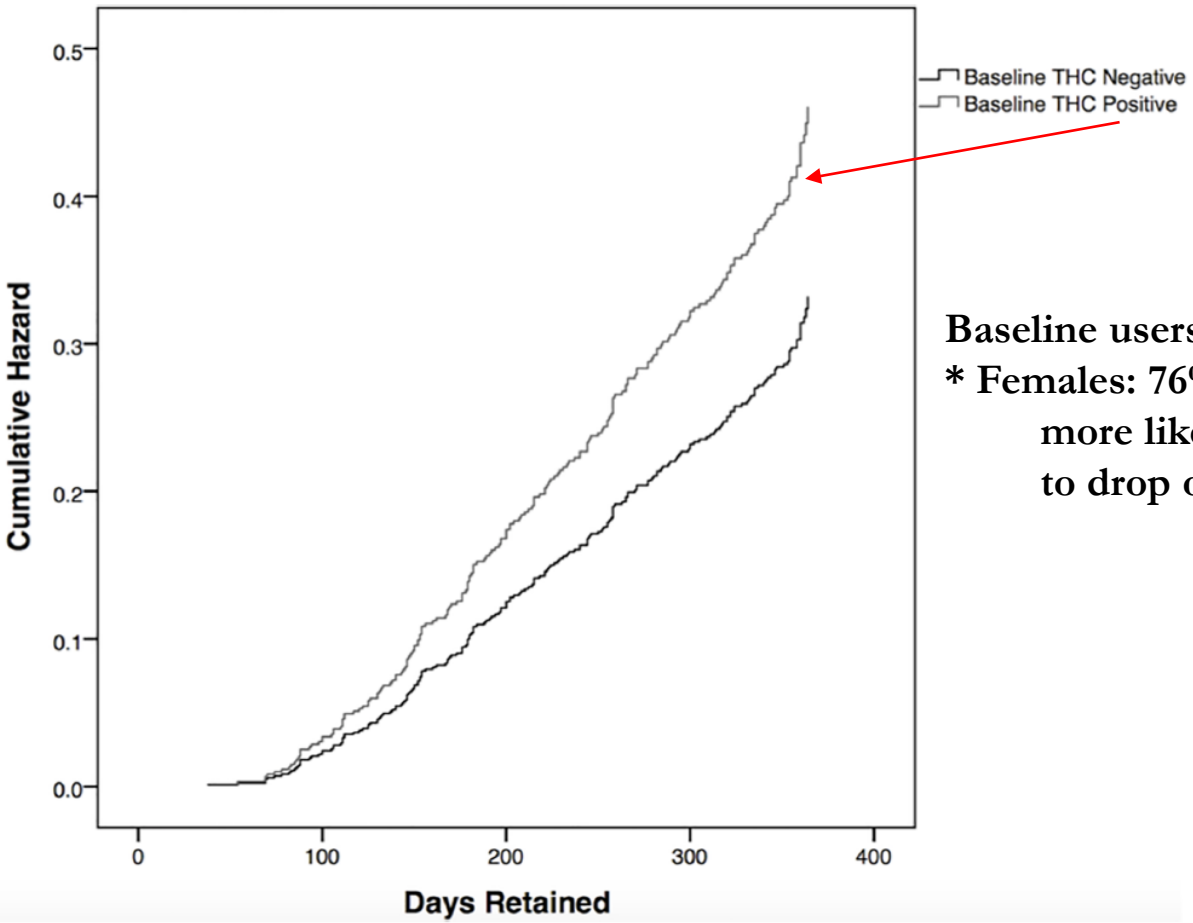
Cohort Study

644 pts

RESEARCH ARTICLE

The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada

Alexandra M. Franklyn[1], Joseph K. Eibl[1], Graham J. Gauthier[1], David C. Marsh[1,2]*



Baseline users:
*** Females: 76% more likely to drop out**

Fig 1. Likelihood of treatment dropout by baseline cannabis use. A Cox proportional hazard analysis was used to characterize the time to treatment discontinuation between the patient groups. Baseline cannabis users were 38.9% more likely to drop out of treatment than baseline non-users [$_{a}$HR = 1.389 (95% CI 1.0573–1.83)].

Check for updates

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Citation: Franklyn AM, Eibl JK, Gauthier GJ, Marsh DC (2017) The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS ONE 12(11): e0187633. https://doi.org/10.1371/journal.pone.0187633

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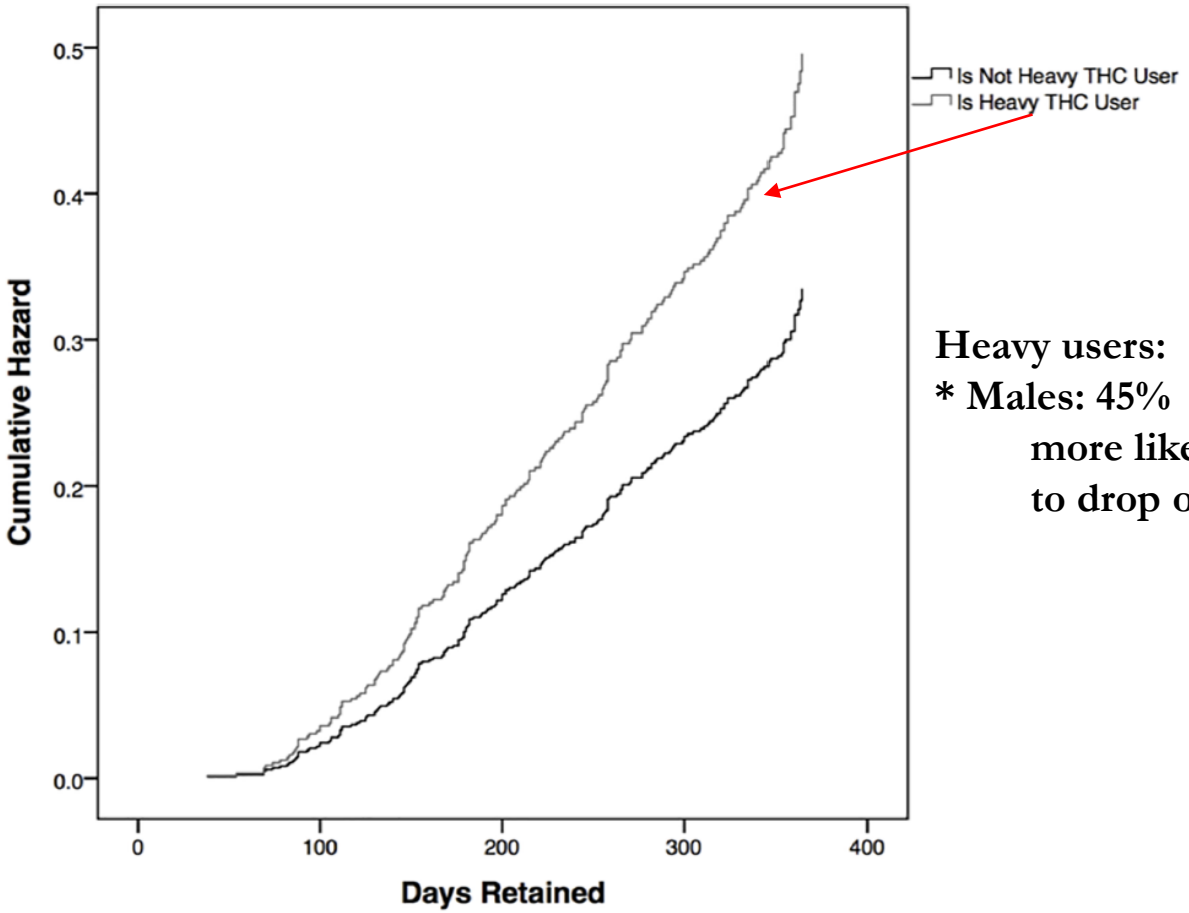

Heavy users:
*** Males: 45% more likely to drop out**

Fig 2. Likelihood of treatment dropout by proportion of cannabis-positive urine samples. A Cox proportional hazard analysis was used to characterize the time to treatment discontinuation between the patient groups. Heavy cannabis users were 48.1% more likely to drop out of treatment than non-heavy users [$_{a}$HR = 1.481 (95% CI 1.134–1.933)].

Check for updates

OPEN ACCESS

Citation: Franklyn AM, Eibl JK, Gauthier GJ, Marsh DC (2017) The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS ONE 12(11): e0187633. https://doi.org/10.1371/journal.pone.0187633

The Journal of Pain, Vol 9, No 3 (March), 2008: pp 254-264
Available online at www.sciencedirect.com

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Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy

Sanjeet Narang,* Daniel Gibson,* Ajay D. Wasan,*,† Edgar L. Ross,* Edward Michna,* Srdjan S. Nedeljkovic,* and Robert N. Jamison*,†

**Department of Anesthesiology, Perioperative, and Pain Medicine and †Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.*

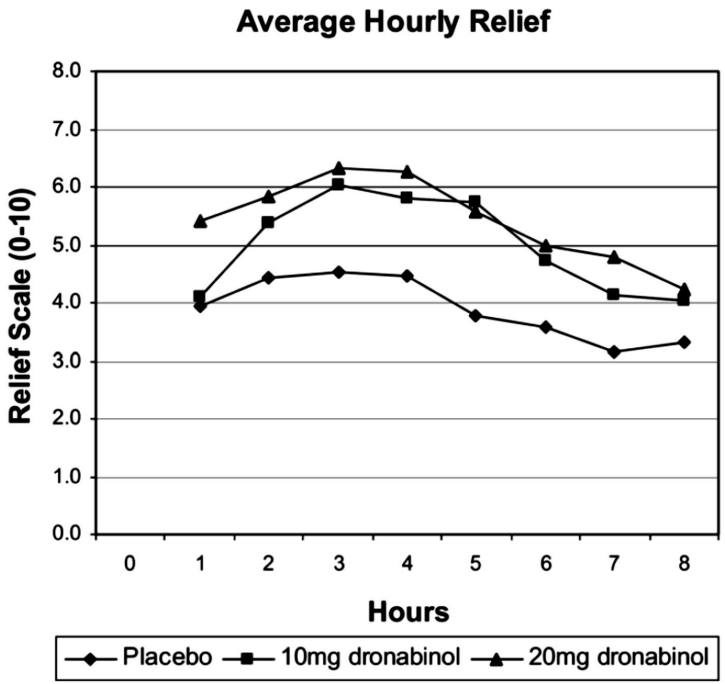

Figure 3. Average hourly pain relief in subjects receiving either dronabinol (10 mg or 20 mg) or placebo (Phase I trial; $P < .01$).

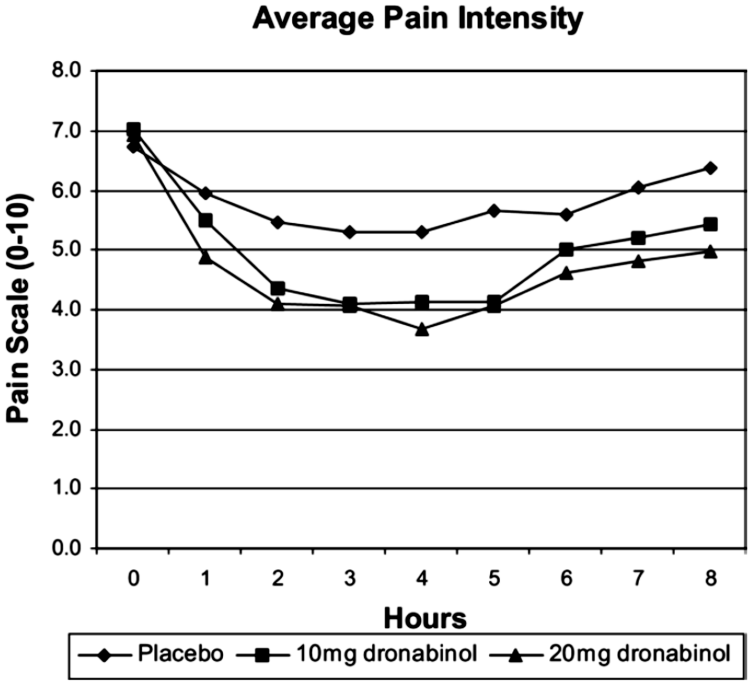

Figure 4. Average hourly pain intensity ratings for subjects receiving dronabinol or placebo (Phase I trial; $P < .001$).

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The Journal of Pain, Vol ■, No ■ (■), 2016: pp 1-6
Available online at www.jpain.org and www.sciencedirect.com

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

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†Om of Medicine, Ann Arbor, Michigan.
‡Departments of Anesthesiology, Medicine (Rheumatology), and Psychiatry, Medical School, University of Michigan, Ann Arbor, Michigan.
§Chronic Pain and Fatigue Research Center, Medical School, University of Michigan, Ann Arbor, Michigan.

Abstract: **Opioids are commonly used to treat patients with chronic pain (CP), though there is little evidence that they are effective for long term CP treatment. Previous studies reported strong associations between passage of medical cannabis laws and decrease in opioid overdose statewide. Our aim was to examine whether using medical cannabis for CP changed individual patterns of opioid use. Using an online questionnaire, we conducted a cross-sectional retrospective survey of 244 medical cannabis patients with CP who patronized a medical cannabis dispensary in Michigan between November 2013 and February 2015. Data collected included demographic information, changes in opioid use, quality of life, medication classes used, and medication side effects before and after initiation of cannabis usage. Among study participants, medical cannabis use was associated with a 64% decrease in opioid use (n = 118), decreased number and side effects of medications, and an improved quality of life (45%). This study suggests that many CP patients are essentially substituting medical cannabis for opioids and other medications for CP treatment, and finding the benefit and side effect profile of cannabis to be greater than these other classes of medications. More research is needed to validate this finding.**

Perspective: ***This article suggests that using medical cannabis for CP treatment may benefit some CP patients. The reported improvement in quality of life, better side effect profile, and decreased opioid use should be confirmed by rigorous, longitudinal studies that also assess how CP patients use medical cannabis for pain management.***

Key words: *Medical cannabis, opioids, chronic pain, side effects.*

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The Journal of Pain, Vol ■, No ■ (■), 2016: pp 1-6
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Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of

Table 4. Outcomes of Interest in the Study Population

Outcome of Interest	*CP (N = 185)*
FM score	9.16 (5.42) n = 185
Opioid use change (−100% to +100%)	−64% (45%) n = 118
Degree to which side effects of medication affect daily function before using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	6.51 (2.88) n = 136
Degree to which side effects of medication affect daily function after using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	2.79 (2.39) n = 136
Change in medication side effects after initiation of cannabis	−3.72 (3.42) n = 136
Number of medication classes used (before cannabis use)	2.38 (1.44) n = 184
Number of medication classes used (after cannabis use)	1.81 (.95) n = 184
Change in quality of life (−100% to +100%)	+45% (29%) n = 180

CP patients. The reported improvement in quality of life, better side effect profile, and decreased opioid use should be confirmed by rigorous, longitudinal studies that also assess how CP patients use medical cannabis for pain management.

Key words: *Medical cannabis, opioids, chronic pain, side effects.*

Lucas *Harm Reduction Journal* (2017) 14:58
DOI 10.1186/s12954-017-0183-9

Harm Reduction Journal

COMMENTARY Open Access

Rationale for cannabis-based interventions in the opioid overdose crisis

Philippe Lucas[1,2,3]

Abstract

Background: North America is currently in the grips of a crisis rooted in the use of licit and illicit opioid-based analgesics. Drug overdose is the leading cause of accidental death in Canada and the US, and the growing toll of opioid-related morbidity and mortality requires a diversity of novel therapeutic and harm reduction-based interventions. Research suggests that increasing adult access to both medical and recreational cannabis has significant positive impacts on public health and safety as a result of *substitution effect*. Observational and epidemiological studies have found that medical cannabis programs are associated with a reduction in the use of opioids and associated morbidity and mortality.

Aims and Methods: This paper presents an evidence-based rationale for cannabis-based interventions in the opioid overdose crisis informed by research on *substitution effect*, proposing three important windows of opportunity for cannabis for therapeutic purposes (CTP) to play a role in reducing opioid use and interrupting the cycle towards opioid use disorder: 1) prior to opioid introduction in the treatment of chronic pain; 2) as an opioid reduction strategy for those patients already using opioids; and 3) as an adjunct therapy to methadone or suboxone treatment in order to increase treatment success rates. The commentary explores potential obstacles and limitations to these proposed interventions, and as well as strategies to monitor their impact on public health and safety.

Conclusion: The growing body of research supporting the medical use of cannabis as an adjunct or substitute for opioids creates an evidence-based rationale for governments, health care providers, and academic researchers to consider the implementation and assessment of cannabis-based interventions in the opioid crisis.

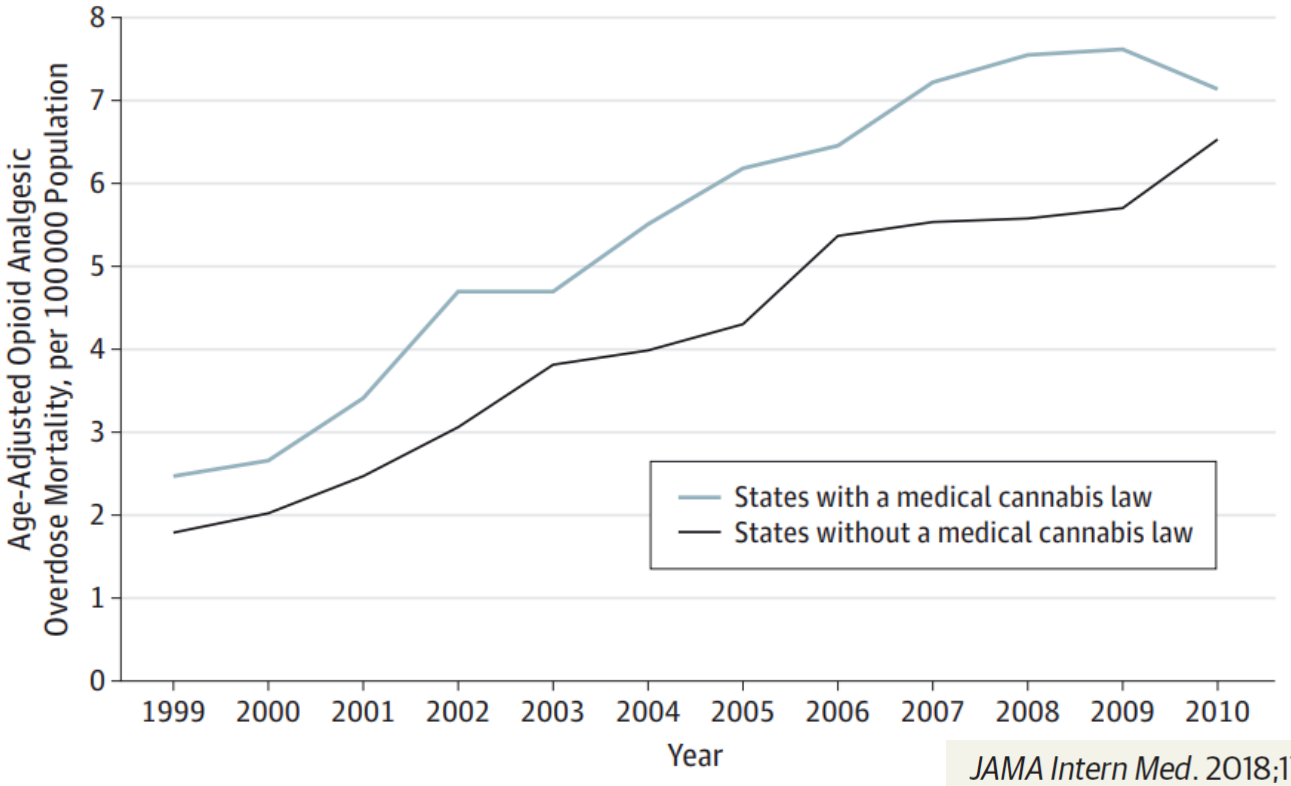
Keywords: Addiction, Opioids, Cannabis, Marijuana, Substitution, Harm reduction

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population

Ashley C. Bradford, BA; W. David Bradford, PhD; Amanda Abraham, PhD; Grace Bagwell Adams, PhD

Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate



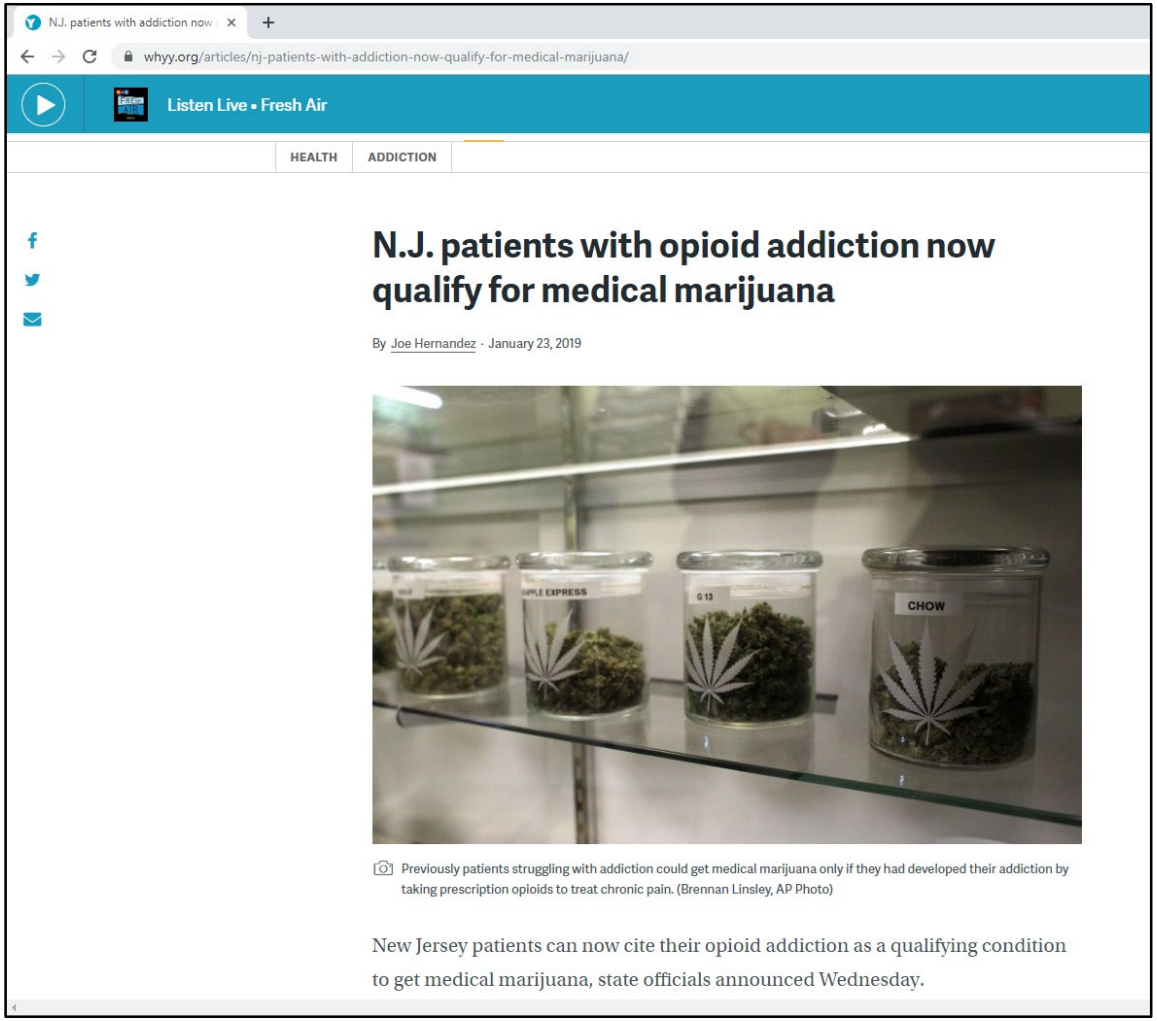
JAMA Intern Med. 2018;178(5):667-673.

These states currently allow "Opioid Use Disorder" as a qualifying condition for medical marijuana:

a. Nevada

b. New Jersey

c. Pennsylvania



Thank you