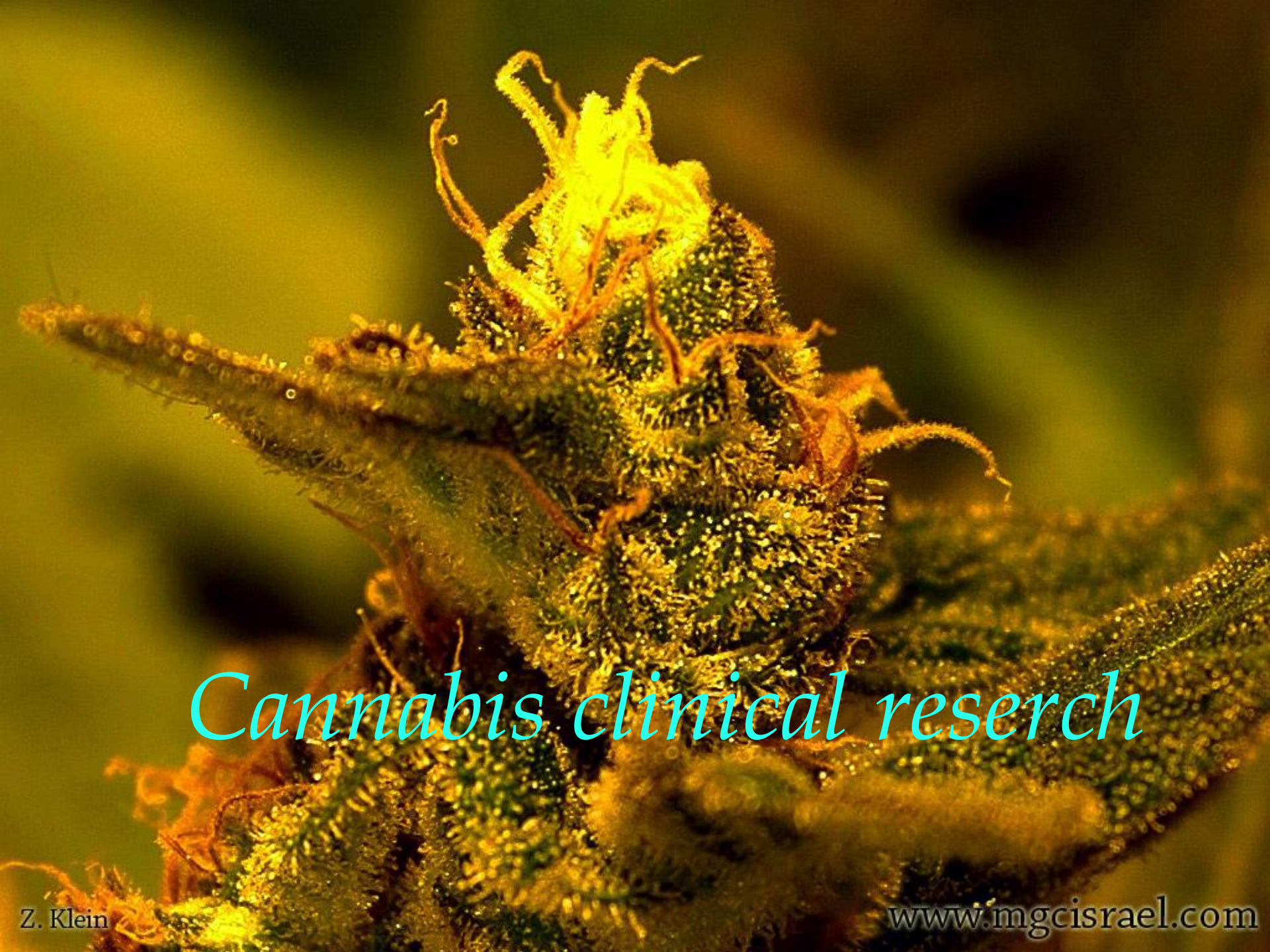
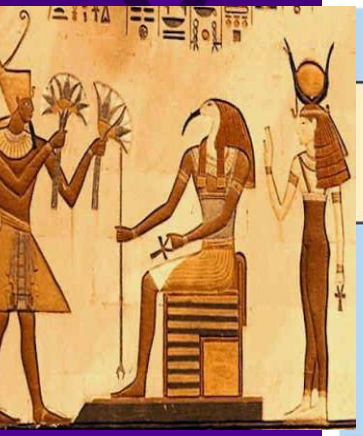
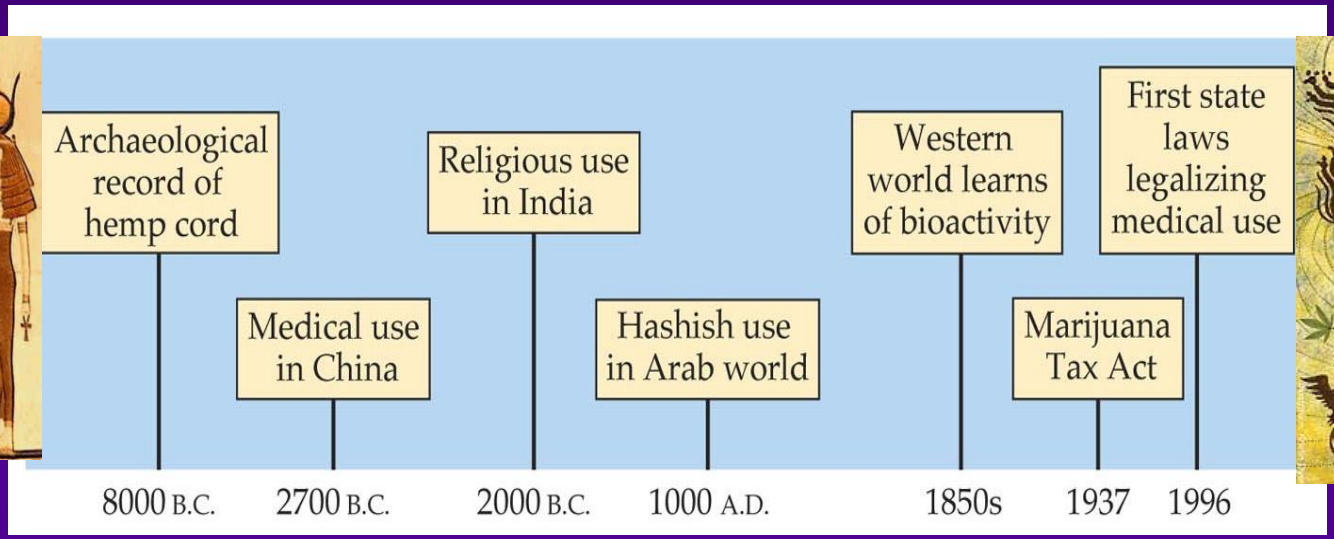

Cannabis clinical reserch
Z. Klein
www.mgcisrael.com

History of Cannabis





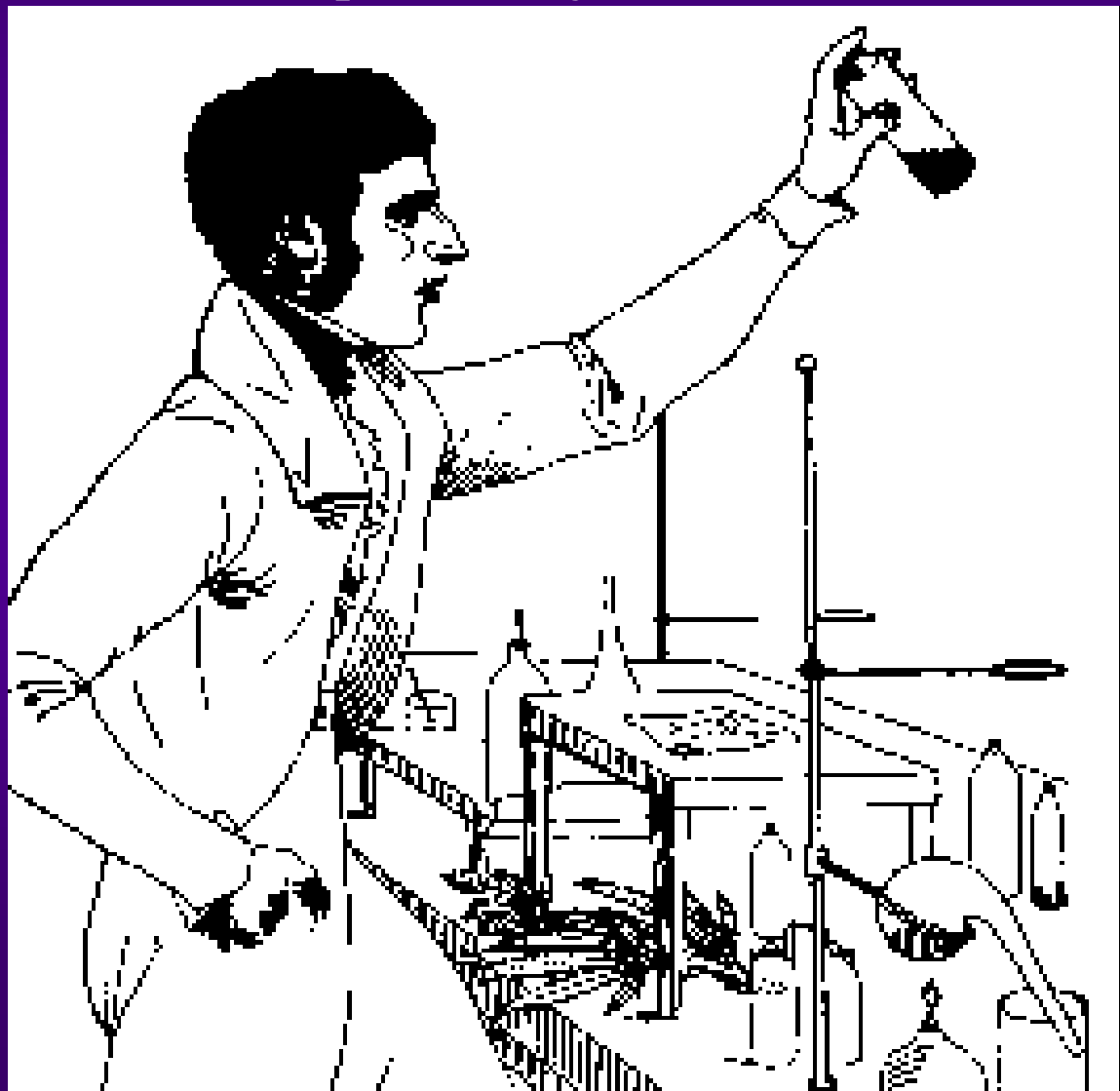
Fibre evidence suggests use of hemp at least 8000 B.C.

Jacques-Joseph Mareau: Physician founded the "Club of the Hashish Eaters" in Paris
Notable "Eaters": Victor Hugo, Alexandre Dumas

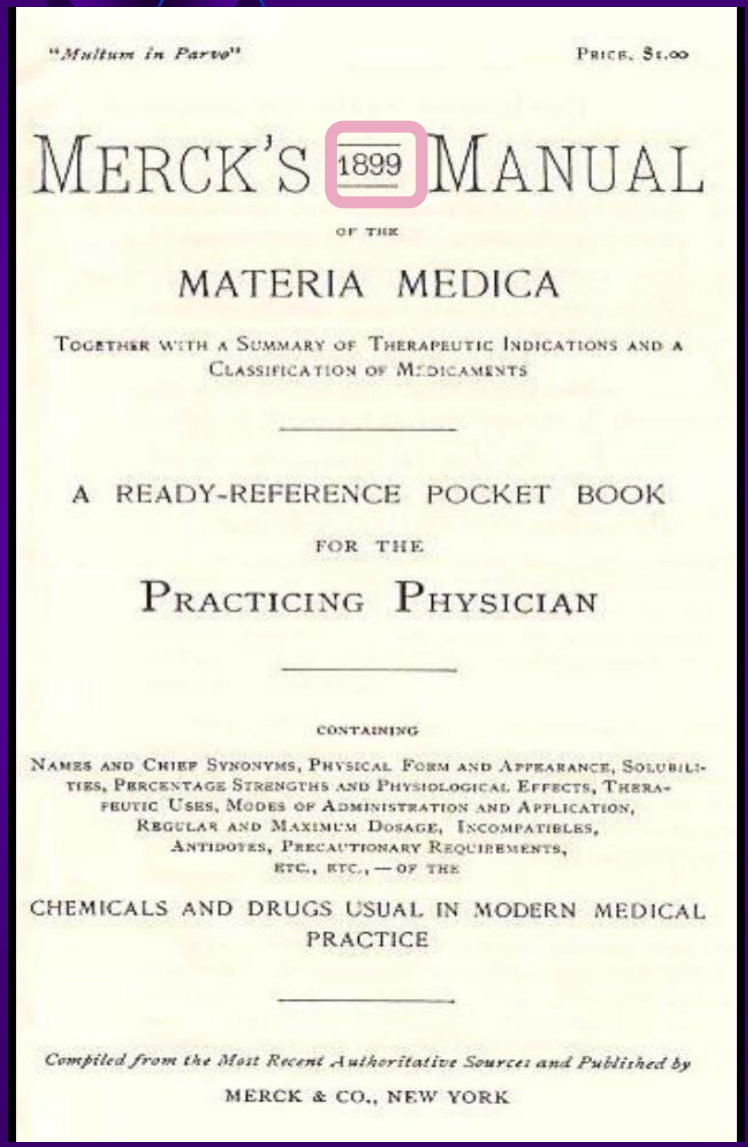
Jews used cannabis (Exodus (30:22-23)
"God told Moses to make holy oil containing cannabis"

William B. O'Shaughnessy

"on the Preparations of the Indian Hemp, or Gunjah" 1839



Cannabis has been utilized in one form or another for treatment of pain for longer than written history.



"Multum in Parvo" PRICE, $1.00

MERCK'S 1899 MANUAL

OF THE

MATERIA MEDICA

TOGETHER WITH A SUMMARY OF THERAPEUTIC INDICATIONS AND A CLASSIFICATION OF MEDICAMENTS

A READY-REFERENCE POCKET BOOK

FOR THE

PRACTICING PHYSICIAN

CONTAINING

NAMES AND CHIEF SYNONYMS, PHYSICAL FORM AND APPEARANCE, SOLUBILITIES, PERCENTAGE STRENGTHS AND PHYSIOLOGICAL EFFECTS, THERAPEUTIC USES, MODES OF ADMINISTRATION AND APPLICATION, REGULAR AND MAXIMUM DOSAGE, INCOMPATIBLES, ANTIDOTES, PRECAUTIONARY REQUIREMENTS, ETC., ETC., — OF THE

CHEMICALS AND DRUGS USUAL IN MODERN MEDICAL PRACTICE

Compiled from the Most Recent Authoritative Sources and Published by

MERCK & CO., NEW YORK

Merck's Manual of the Materia Medica
First Edition: 1899

Prescribed Uses Of Cannabis Indica

Albuminuria
Ascites
Asthma
Bladder, Irritable
Bright's Disease, Acute
Bright's Disease, Chronic
Bronchitis, Chronic
Cholera Asintica
Chordee
Chorea
Climacteric Disorders
Corns
Coughs
Cystitis
Delerium
Delerium Tremens
Diarrhea
Dropsy
Dysmenorrhea
Dyspepsia
Dysuria
Epilepsy
Exophthalmos
Gastralgia
Gastric Ulcer
Gonorrhea
Headache
Hematuria
Hemicrania
Hiccough
Hydrophobia
Hysteria
Impotence
Inflammation
Influenza
Insomnia
Labor
Locomotor Ataxia
Mania
Melancholia
Mennorrhagia
Metrorrhagia
Migraine
Nephritis, Acute
Neuralgia
Opium Habit
Ovarian Neuralgia
Ovaritis
Pain
Paralysis Agitans
Paralysis and Paresis
Phthisis
Sea-Sickness
Tetanus
Tic Douloureux
Trismus
Uterine Cancer

Courtesy of ***The Cannabis Consultants***

Why it became prohibited?

1930s: **Harry Anslinger**

1937: Marijuana Tax Act

First Commissioner of the U.S. Treasury Department's Federal Bureau of Narcotics (1930-1962)

Beware! Young and Old—People in All Walks of Life!

This may be handed you by the friendly stranger. It contains the Killer Drug "Marihuana"-- a powerful narcotic in which lurks

Murder! Insanity! Death!

WARNING!

Dope peddlers are shrewd! They may put some of this drug in the

or in the [illegible] **or in the tobacco cigarette.**

WRITE FOR DETAILED INFORMATION, ENCLOSING 12 CENTS IN POSTAGE—MAILING COST

Address: THE INTER-STATE NARCOTIC ASSOCIATION

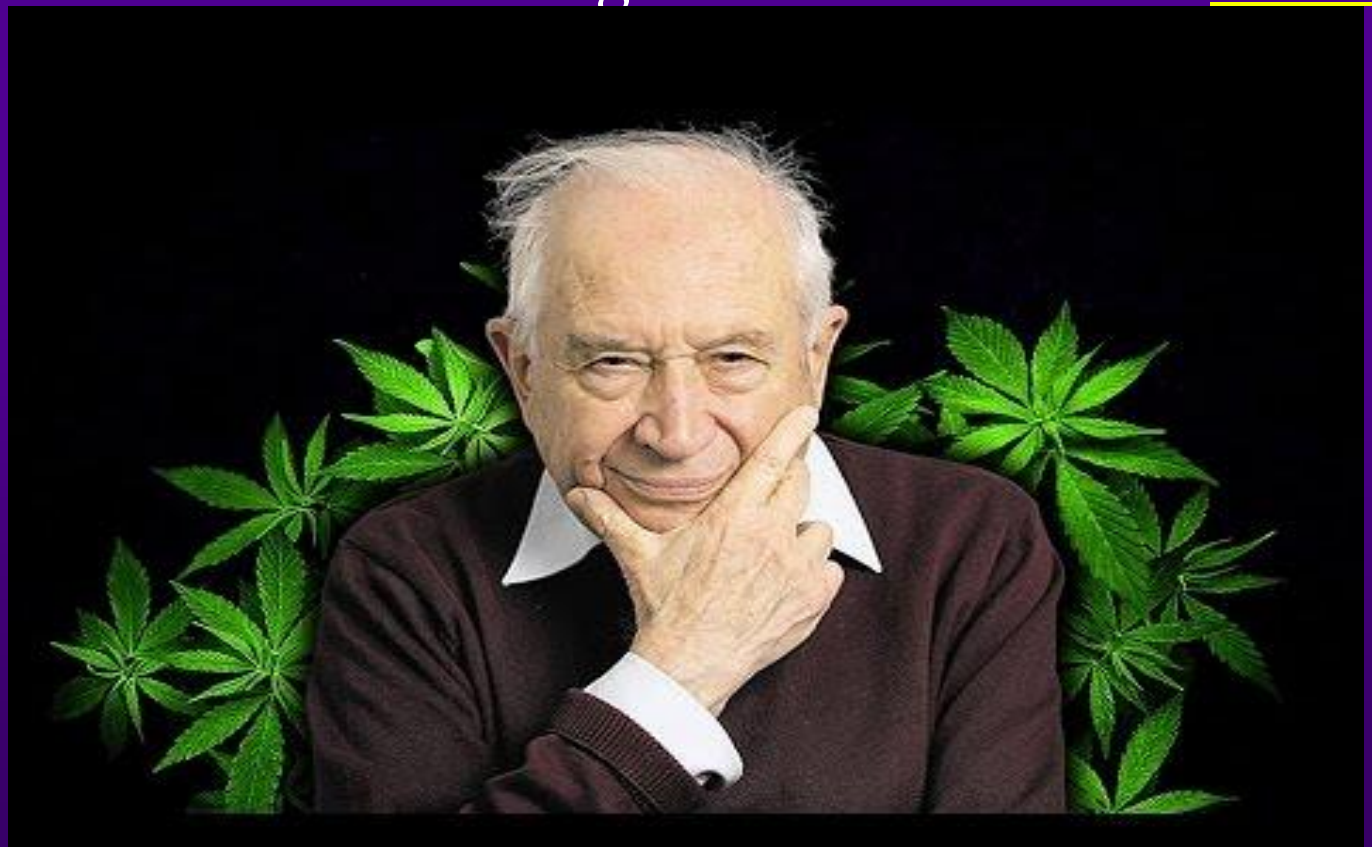
(Incorporated not for profit)

53 W. Jackson Blvd. Chicago, Illinois, U. S. A.

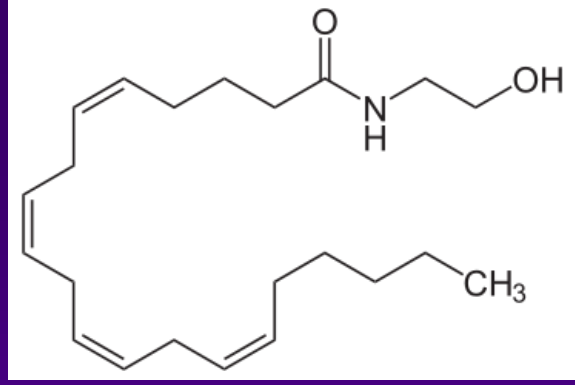
The endogenous cannabinoid system might have evolved millions of years before the evolution of the *Cannabis* plant itself

Rafael Mechoulam

Best known for his work in the isolation, and synthesis of Δ^9-tetrahydrocannabinol, and for the isolation and the identification of the endogenous cannabinoids anandamide.



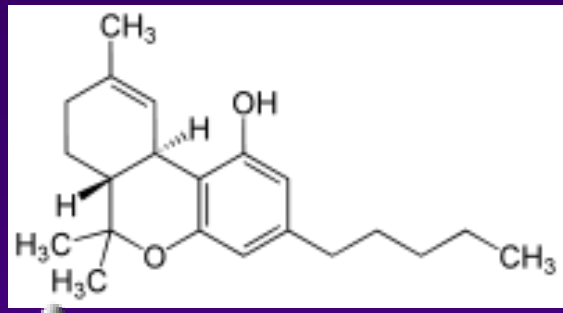
Anandamid

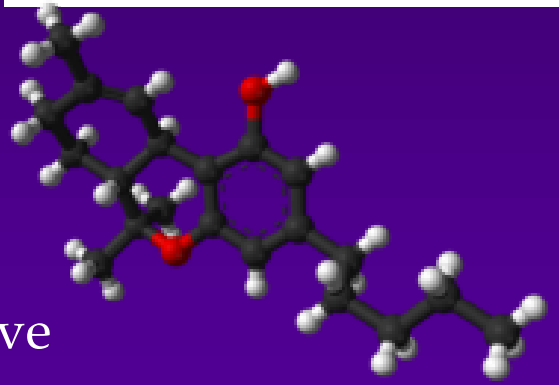


- In 1992, in Raphael Mechoulam's lab, the first such compound was identified as arachidonoyl ethanolamine and named anandamide,
- a name derived from the Sanskrit word for bliss and -*amide*.
- Anandamide is derived from the essential fatty acid arachidonic acid.
- Anandamide binds to the central (CB_1) and, to a lesser extent, peripheral (CB_2) cannabinoid receptors, where it acts as a partial agonist. Anandamide is about as potent as THC at the CB_1 receptor
- This endocannabinoid mediated system permits the postsynaptic cell to control its own incoming synaptic traffic.
- Activation of cannabinoid receptors temporarily reduces the amount of conventional neurotransmitter released

Tetrahydrocannabinol

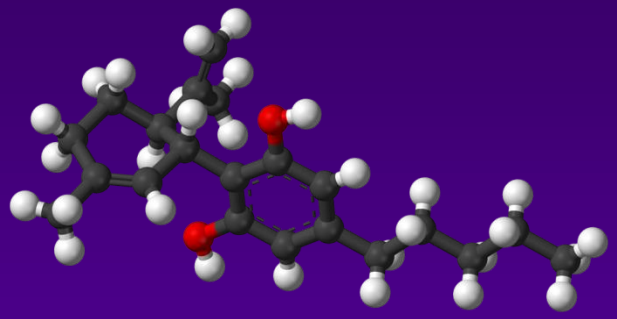
THC

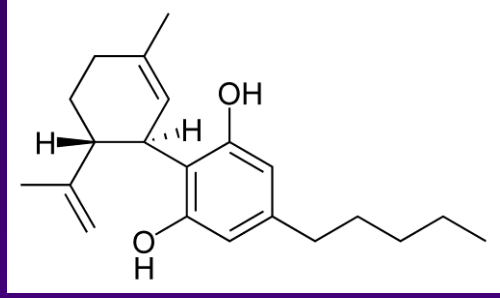




Tetrahydrocannabinol (THC) is the primary psychoactive component of the Cannabis plant. *Delta*-9-tetrahydrocannabinol (Δ^9-THC, THC) and *delta*-8-tetrahydrocannabinol (Δ^8-THC), mimic the action of anandamide, a neurotransmitter produced naturally in the body. These two THC's produce the effects associated with cannabis by binding to the CB_1 cannabinoid receptors in the brain. THC appears to ease moderate pain (analgesic) and to be neuroprotective. Studies show THC reduces neuroinflammation and stimulates neurogenesis.[15][16][17] THC has approximately equal affinity for the CB_1 and CB_2 receptors.[18]

CANNBIDIOL
CBD





- Cannabidiol (CBD) is not psychoactive, and was thought not to affect the psychoactivity of THC However, recent evidence shows that smokers of cannabis with a higher CBD/THC ratio were less likely to experience schizophrenia-like symptoms
- Cannabidiol has little affinity for CB_1 and CB_2 receptors but acts as an indirect antagonist of cannabinoid agonists
- It appears to relieve convulsion, inflammation, anxiety, and nausea. CBD has a greater affinity for the CB_2 receptor than for the CB_1 receptor
- Cannabidiol has also been shown to act as a $5\text{-}HT_{1A}$ receptor agonist,[24] an action that is involved in its antidepressant,[25][26] anxiolytic,[26][27] and neuroprotective[28][29] effects

The Human Endocannabinoid System

THC and CBN are known to "fit" like lock and key into network of existing receptors . The Endocannabinoid System exists to receive cannabinoids produced inside the body called "Anadnamide" and "2-Arachidonyl-glycerol". Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.

CB1 receptors are concentrated in the brain and central nervous system but also sparsely populates other parts of the human body.

Receptors are found on cell surfaces

THC

Tetrahydrocannibinol

CB1

CBD

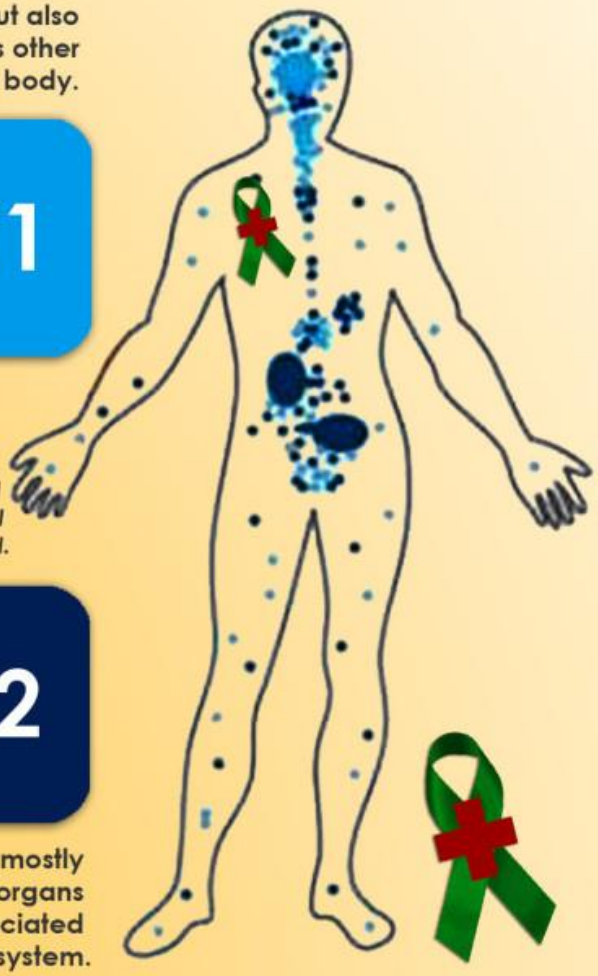
Cannabidiol

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

CBN

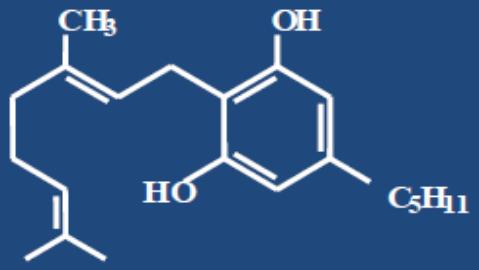
Cannabinol

CB2

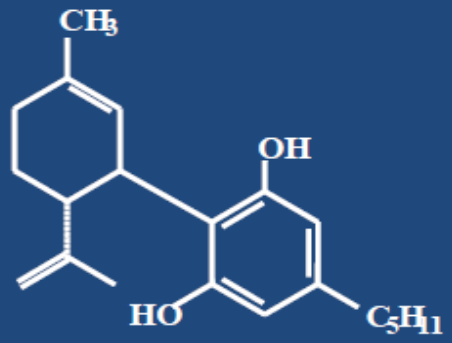


CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

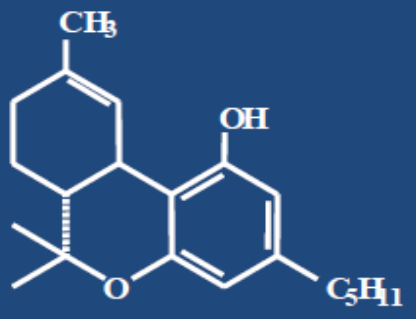
www.the-human-solution.org



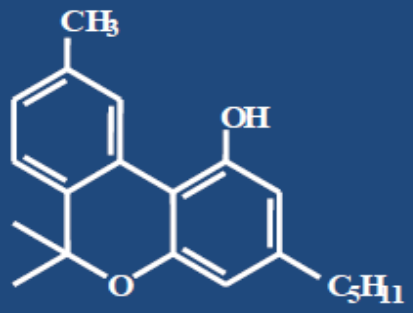
cannabigerol (CBG)
(Gaoni and Mechoulam, 1964)



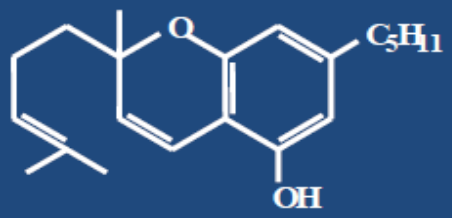
cannabidiol (CBD)
(Mechoulam and Shvo, 1963)



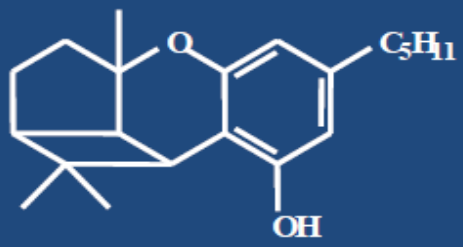
Δ^9-tetrahydrocannabinol (Δ^9-THC)
(Gaoni and Mechoulam, 1964)



cannabinol (CBN)
(Adams et al., 1940)



cannabichromene (CBC)
(Claussen et al., 1966;
Mechoulam and Gaoni, 1966)



cannabicyclol (CBL)
(Crombie et al., 1968)

Representative natural cannabinoids

More then 113 Cannabinoids and over 100 Terpenes

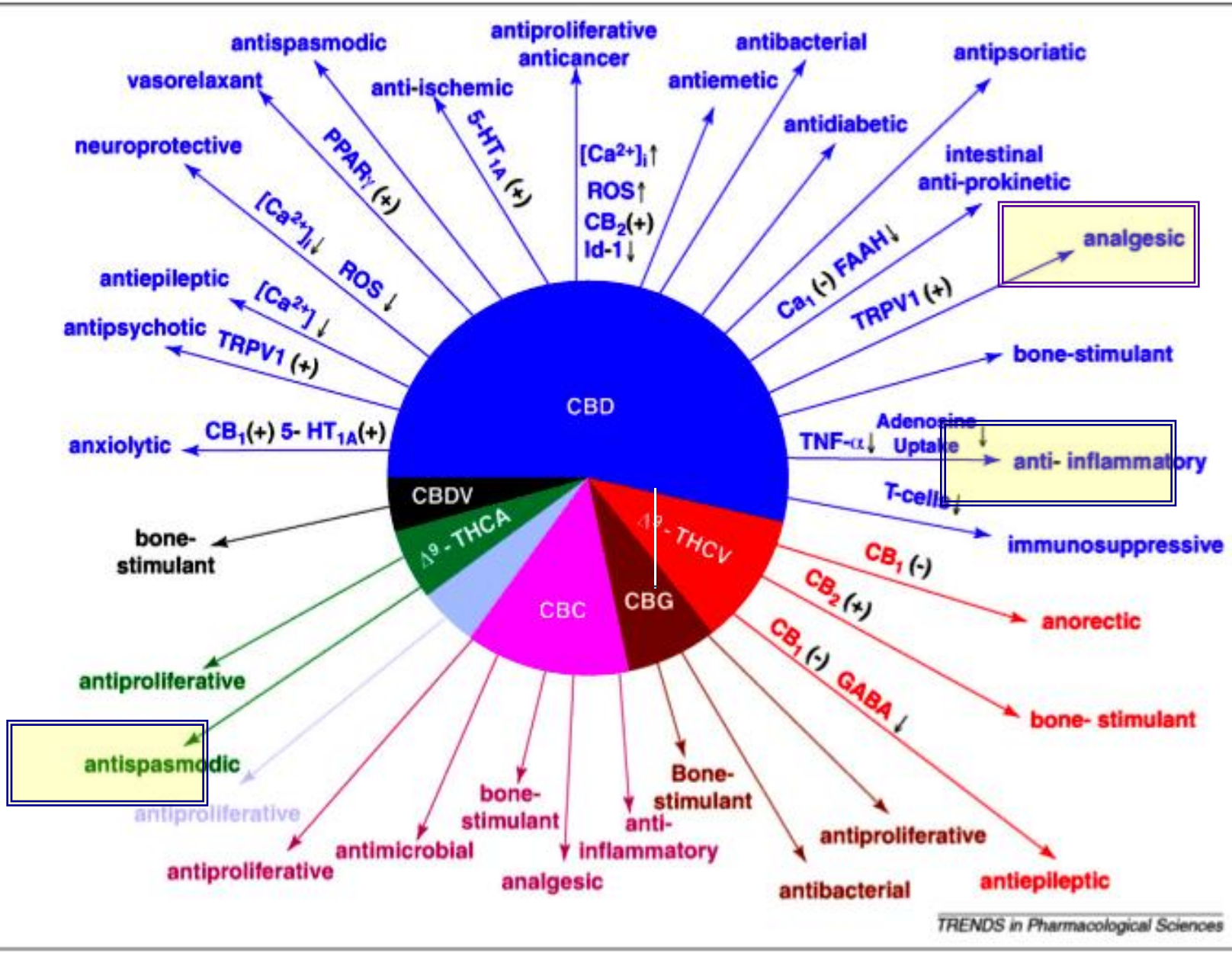


Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT_{1A}, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.

520 AD

Proven cannabis indication?

- Hunger stimulation for wasting syndrome
- Anti-emetic and anti-nausea properties in AIDS or cancer chemotherapy
- Anti-spasmotic properties for MS
- Epilepsy and other neurological dysfunctions
- Reducing intra-ocular eye pressure in glaucoma
- Analgesic properties in a large number of chronic conditions.


Z.KLEIN
www.mgcisrael.com

Cannabis medical research

- Every year there are dozens of cannabis research articles
- Mainly basic science and clinical case reports
- Most articles regarding cannabis addiction and side effects (Psychosis, COPD, Schizophrenia, Atherosclerosis, CVA and more)
- All most no good efficacy “double blind randomized placebo controlled”

66 Studies found for: **cannabis | Interventional Studies | pain | Start date from 01/01/2000 to 01/01/**

Applied Filters:
☑ **Interventional**

List | By Topic | On Map | Search Details

Terms and Synonyms Searched:

Terms Synonyms	Search Results*	Entire Database**
cannabis	66 studies	820 studies
Marihuana	22 studies	521 studies
Sativex	21 studies	57 studies
Pot	4 studies	56 studies
Hash	2 studies	14 studies
Weed	--	26 studies
pain	66 studies	16,724 studies
Painful	6 studies	527 studies
AChE	--	27 studies
Dolor	--	6 studies

Terms and Synonyms Searched:

Terms Synonyms	Search Results*	Entire Database**
cannabis	39 studies	820 studies
Sativex	20 studies	57 studies
Marihuana	13 studies	521 studies
Pot	2 studies	56 studies
Hash	1 studies	14 studies
Weed	--	26 studies
pain	39 studies	16,724 studies
Painful	4 studies	527 studies
AChE	--	27 studies
Dolor	--	6 studies

-- No studies found

* Number of studies in the search results containing the term or synonym

** Number of studies in the entire database containing the term or synonym

NIDA NOTES

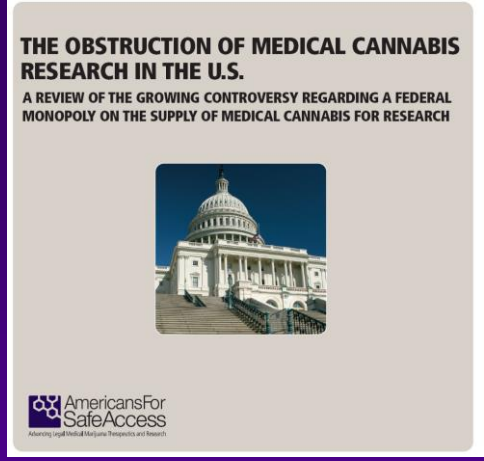
NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

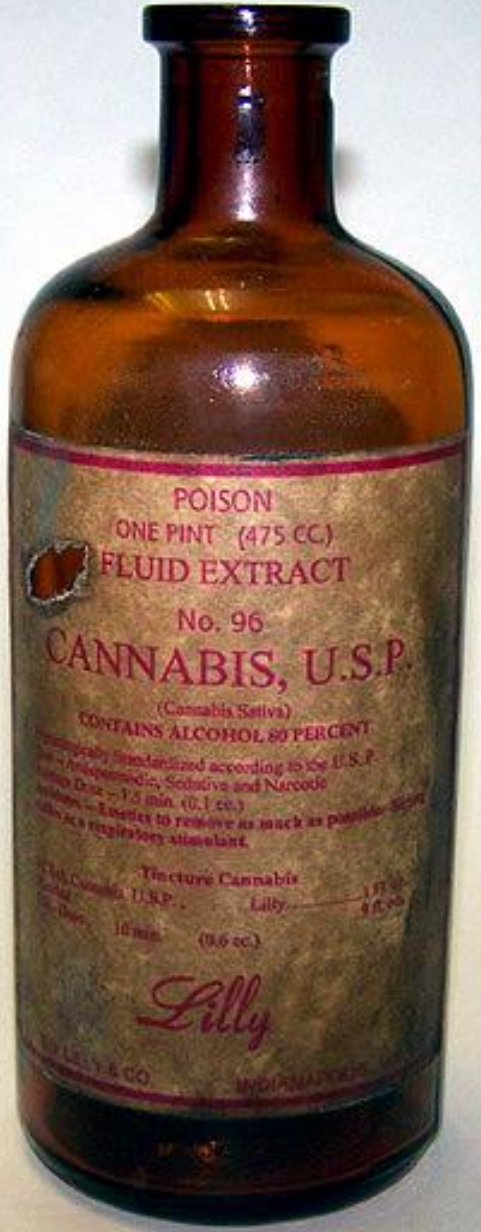
Research on Marijuana

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

FDA Accepts Marijuana for PTSD Protocol



- Although both MAPS and the FDA are satisfied with the protocol design, we cannot begin the study until passes yet another review process with the National Institute on Drug Abuse/Public Health Service (NIDA/PHS). This redundant review, which may take another year or more, is required solely because NIDA has a monopoly on the supply of marijuana for research, and NIDA/PHS must review the protocol before allowing us to purchase marijuana from the agency. NIDA's mission does not include exploring the potential beneficial uses of marijuana.


POISON
ONE PINT (475 CC)
FLUID EXTRACT
No. 96
CANNABIS, U.S.P.
(Cannabis Sativa)
CONTAINS ALCOHOL 80 PERCENT
Tincture Cannabis
Lilly
Lilly

Clinical Cannabis studies

- IRB (Institutional Review Board)
- Basic, animal, safety in human (side effect and risk), efficacy, post marketing/long term
- Prospective
- Interventional (action or medication)
- Subjects consistency
- Indication consistency
- Double blind
- Randomized
- Placebo controlled
- Long term

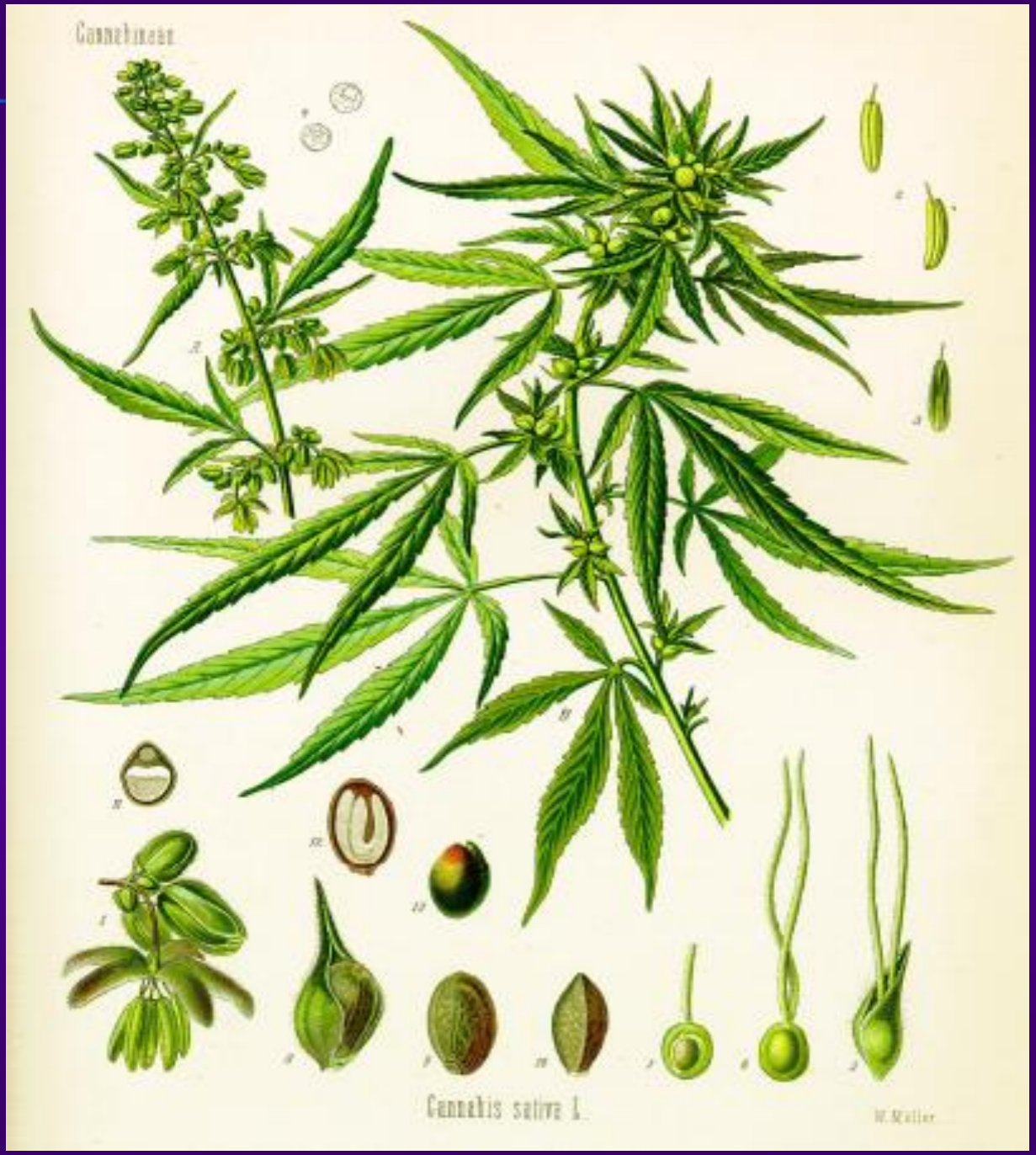

16 Fl. Oz
POISON
TINCTURE
CANNABIS
N. F. VI
ALCOHOL 88 PER CENT
Each 100 cc. represents 10 Gm.
Cannabis sativa.
Average Dose:—15 minims
(1 cc.)
Made in U.S.A. by
SHARP & DOHME
PHILADELPHIA - BALTIMORE

Problematic area in cannabis research

- IRB
  - Difficulty to approve the use of a medication that is not backed by a producer company
  - Approval of a medication that is define by law as a illegal drug
  - Require a national review board approval

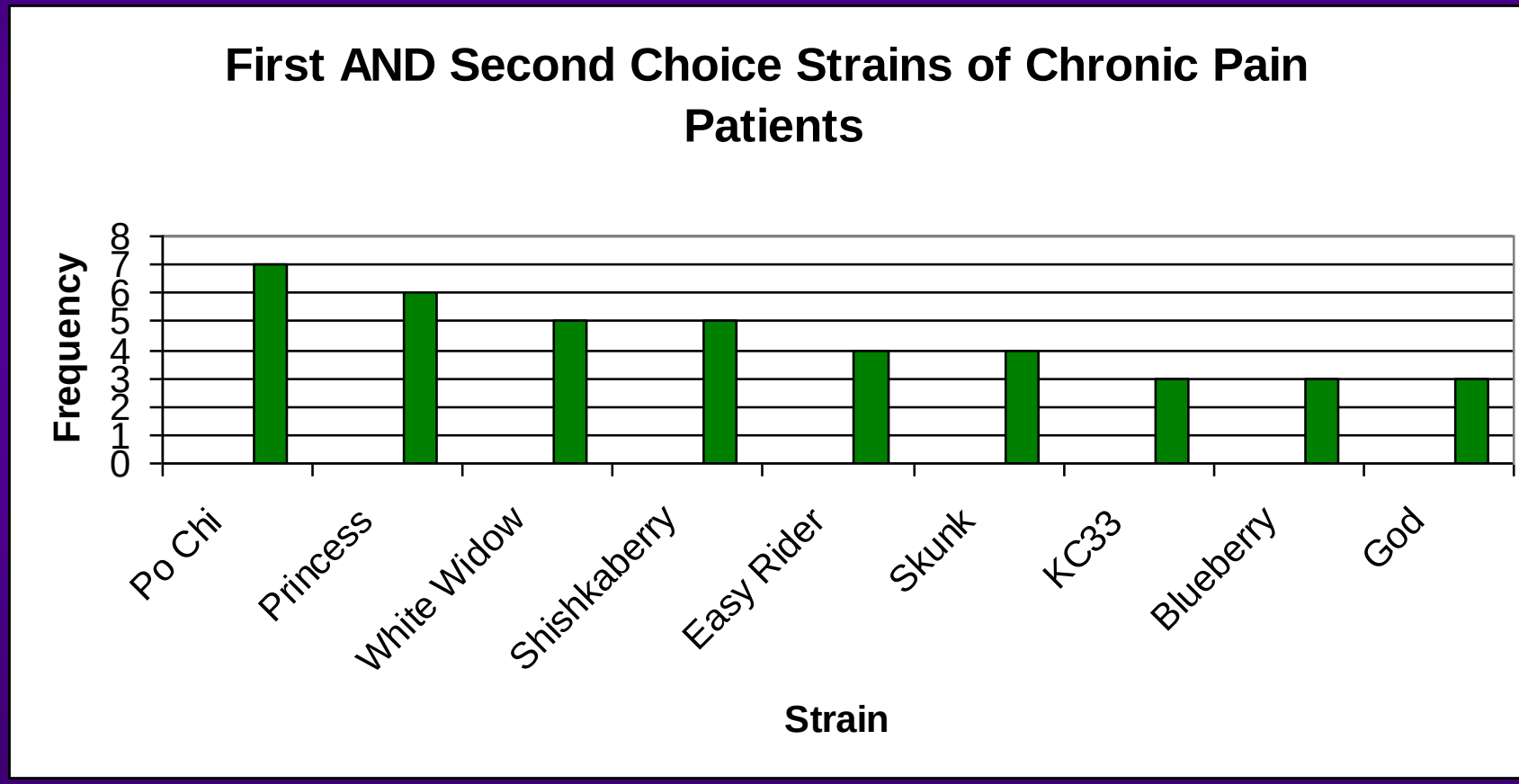
Problematic area in cannabis research suggested solution

- Research and development committee
  - Basic science
  - Clinician
  - Agricultural
  - Industry
  - Administrator
- Designated IRB committee member
- Create specific legislation for cannabis research


Cannabineae
Cannabis sativa L.

Problematic area in cannabis research

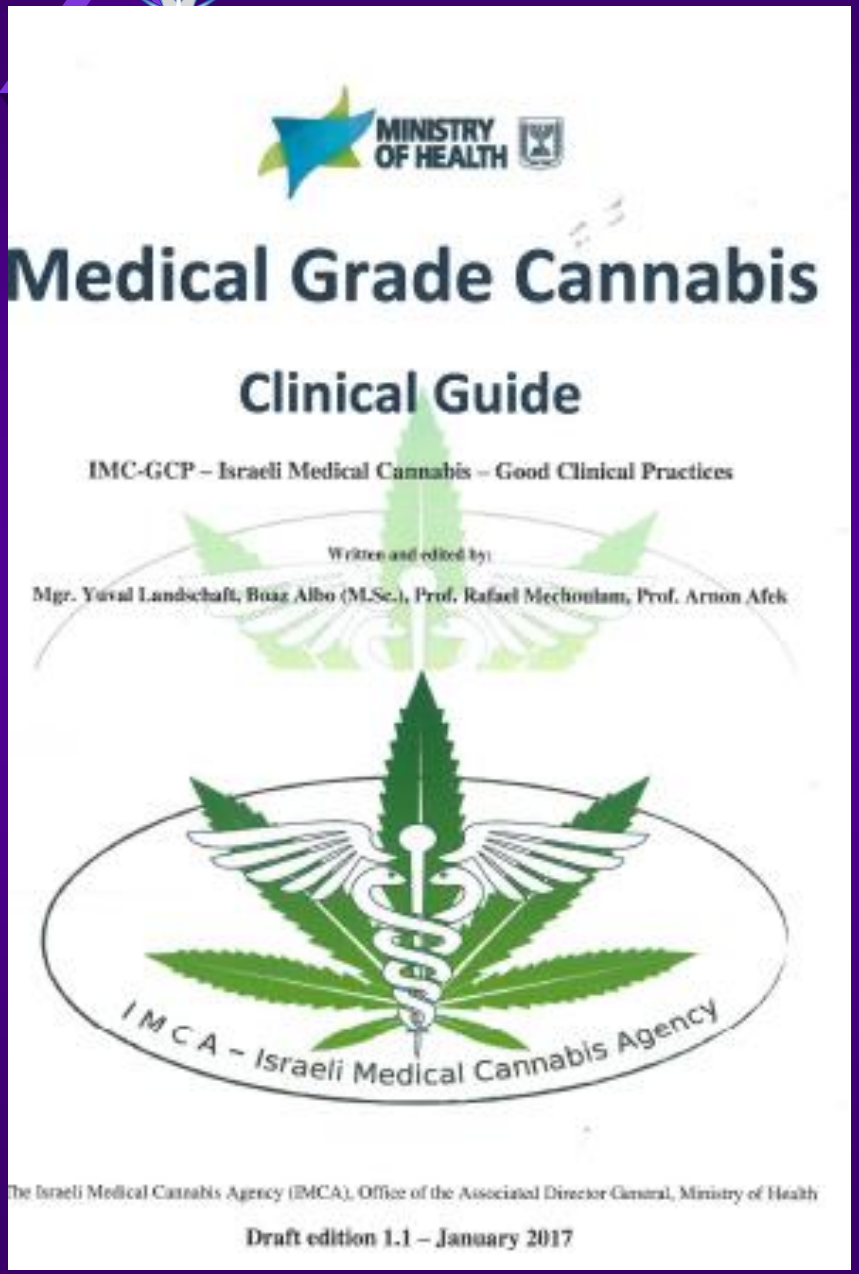
- Medication
  - Cannabis is not a approved medication
  - Consistency of the medication (plant base drug, active ingredients, batch consistency over time)
  - Consistency of intervention (inhaled, smoked, sublingual, eaten, ointment and more)
  - Starting dose and titration

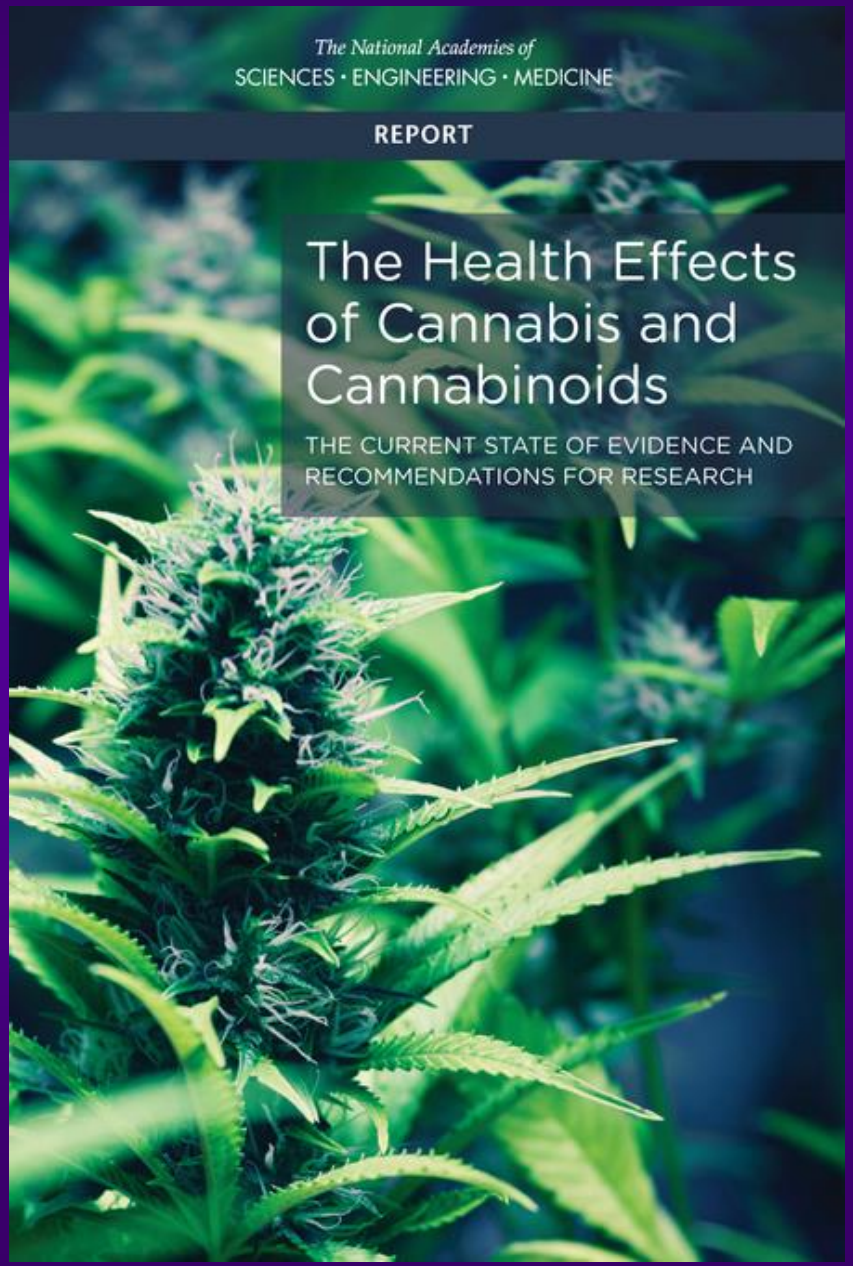

First AND Second Choice Strains of Chronic Pain Patients
Frequency
0
1
2
3
4
5
6
7
8
Po Chi
Princess
White Widow
Shishkaberry
Easy Rider
Skunk
KC33
Blueberry
God
Strain

Problematic area in cannabis research suggested solution

- Building a supply chain that will produce as close to medication as possible.
- Have supervision on the quality of the product. Consistency of the drug.
- Allow the consistency of strain and profile of other cannabinoids
- Build a registry from the beginning of your program

SYSTEMATIC REVIEWS





"שמן קנביס רפואי IMC-Medical Grade":

E.P	Exp.	CBN	CBD	THC	פרי'ס	סוג
8	קר'קוא מנ' שנה	0% (Up to 1.5%)	24% (28% - 20%)	0% (0.5% - 0.0%)	"שמן קנביס רפואי CBD T0 C24"	CBD Rich
7	קר'קוא מנ' שנה	0% (Up to 1.5%)	20% (24% - 16%)	1% (2.5% - 0.0%)	"שמן קנביס רפואי CBD T1/C20"	
5.5	קר'קוא מנ' שנה	0% (Up to 1.5%)	12% (16% - 11%)	3% (5.5% - 0.5%)	"שמן קנביס רפואי CBD T3/C15"	
5	קר'קוא מנ' שנה	0% (Up to 1.5%)	10% (14% - 6%)	5% (7.5% - 2.5%)	"שמן קנביס רפואי CBD T5/C10"	
6.5	קר'קוא מנ' שנה	0% (Up to 1.5%)	10% (14% - 6%)	10% (14% - 6%)	"שמן קנביס רפואי T10/C10"	
4	קר'קוא מנ' שנה	0% (Up to 1.5%)	2% (3.5% - 0.2%)	10% (14% - 6%)	"שמן קנביס רפואי T10/C2"	THC Rich
8	קר'קוא מנ' שנה	0% (Up to 1.5%)	3% (5.5% - 0.5%)	15% (19% - 11%)	"שמן קנביס רפואי T15/C3"	
8	קר'קוא מנ' שנה	0% (Up to 1.5%)	4% (7% - 1%)	20% (24% - 16%)	"שמן קנביס רפואי T20/C4"	

Problematic area in cannabis research

- Medication
  - Consistency of intervention (inhaled, smoked, sublingual, eaten, ointment and more)
  - Most patients prefer smocking
  - Smoking VS PO is inherently different in pharmacology (time to activity, T/2 , metabolites and more)
  - Starting dose and titration

Problematic area in cannabis research suggested solution

- Prefer PO to inhaled or smoked
- Easier to control dose and create placebo
- Prefer inhaled over smoking
- Use smart consistent inhalers
- Synthetic vs plant based medication

Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol.

Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R.

J Pharm Sci. 2006 Jun;95(6):1308-17.

Source

Division of Pharmacognosy, Institute of Biology, Leiden University, Leiden, The Netherlands. ahazekamp@rocketmail.com

Abstract

What is currently needed for optimal use of medicinal cannabinoids is a feasible, nonsmoked, rapid-onset delivery system. Cannabis "vaporization" is a technique aimed at suppressing irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where smoke and associated toxins are produced. The goal of this study was to evaluate the performance of the Volcano vaporizer in terms of reproducible delivery of the bioactive cannabinoid tetrahydrocannabinol (THC) by using pure cannabinoid preparations, so that it could be used in a clinical trial. By changing parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporization of THC was systematically improved to its maximum, while preventing the formation of breakdown products of THC, such as cannabinol or delta-8-THC. Inter- and intra-device variability was tested as well as relationship between loaded- and delivered dose. It was found that an average of about 54% of loaded THC was delivered into the balloon of the vaporizer, in a reproducible manner. When the vaporizer was used for clinical administration of inhaled THC, it was found that on average 35% of inhaled THC was directly exhaled again. Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. The final pulmonal uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking.


with the new VALVE
EASY VALVE (closed)
with mouthpiece
EASY VALVE (opened)
with filling chamber
Diaphragm
Valve housing
Mouthpiece
Balloon jacket
Air flow
Air channel
Temperature sensor
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Specific Medicines.
AMERICAN HEMP.
(CANNABIS SATIVA.)
LLOYD BROTHERS, CINCINNATI, O.
Specific Use: In wakefulness, low mental conditions, and in painful urinary affections.
Dose: ℞. Sp. Med. American Hemp, 3ss to 3j.
Misc. Water, 3iv.
Sig.: A teaspoonful of the dilution every hour. Shake the bottle before giving each dose.
Poisonous in Overdoses.

Problematic area in cannabis research

- Placebo and double blinding
  - Difficulty to hide the psychogenic effect from the subject
  - Difficulty to hide the typical taste and smell of the cannabis
  - Consistency of the placebo and purity
    - Different cannabinoids
    - The effect of the terpenes


CANNABIS FLOS
variëteit
bedrobinol
5 gram
Ministerie van Volksgezondheid, Welzijn en Sport
Bureau voor Medicinale Cannabis
Den Haag

Problematic area in cannabis research suggested solution

- Some companies created a placebo that is without THC or CBD.
- Using intelligent systems that will randomize the medication (Syke)
- Starting cannabis studies early in the establishment of medical cannabis program

syqe

Raw Cannabis

Structural Modification

Preloaded Cartridges

Metered-Dose Delivery

Problematic area in cannabis research

- Choice of subjects
  - Always a problem but more on pain studies
  - Many parallel diagnosis in neuropathic pain
  - Previous experience vs naivety with cannabis
  - Recruitment
  - No gold standards for analgesic efficacy

Problematic area in cannabis research suggested solution

- Starting cannabis studies early in the establishment of medical cannabis program (naivety and ease of recruitment)
- Base studies on non-subjective parameter as possible.
  - Reduction of medication
  - Reduction of medical services use (visits, procedures)
  - Monitoring devices (Actigraf for sleep, monitoring watches for movement and other prameters of HR BP ECG and more

Problematic area in cannabis research

- Drug company
  - Funding
  - Patenting
  - Problematic aspects of cannabis (addiction, schedule 1 drug and more
  - The federal government DEA FDA NIDA

The "big ones" enter into the field

syqe

Selective-dose cannabis inhaler

PANAXIA
Pharmaceutical Industries

Rafa.

TEVA

BOL Pharma
Breath Of Life


MARINOL
An Original
Preparation of
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MARINOL is composed of important principles, organic and inorganic, of certain marine algae—seaweed, moss, and of deep-sea water, with homogenized Cod Liver Oil.
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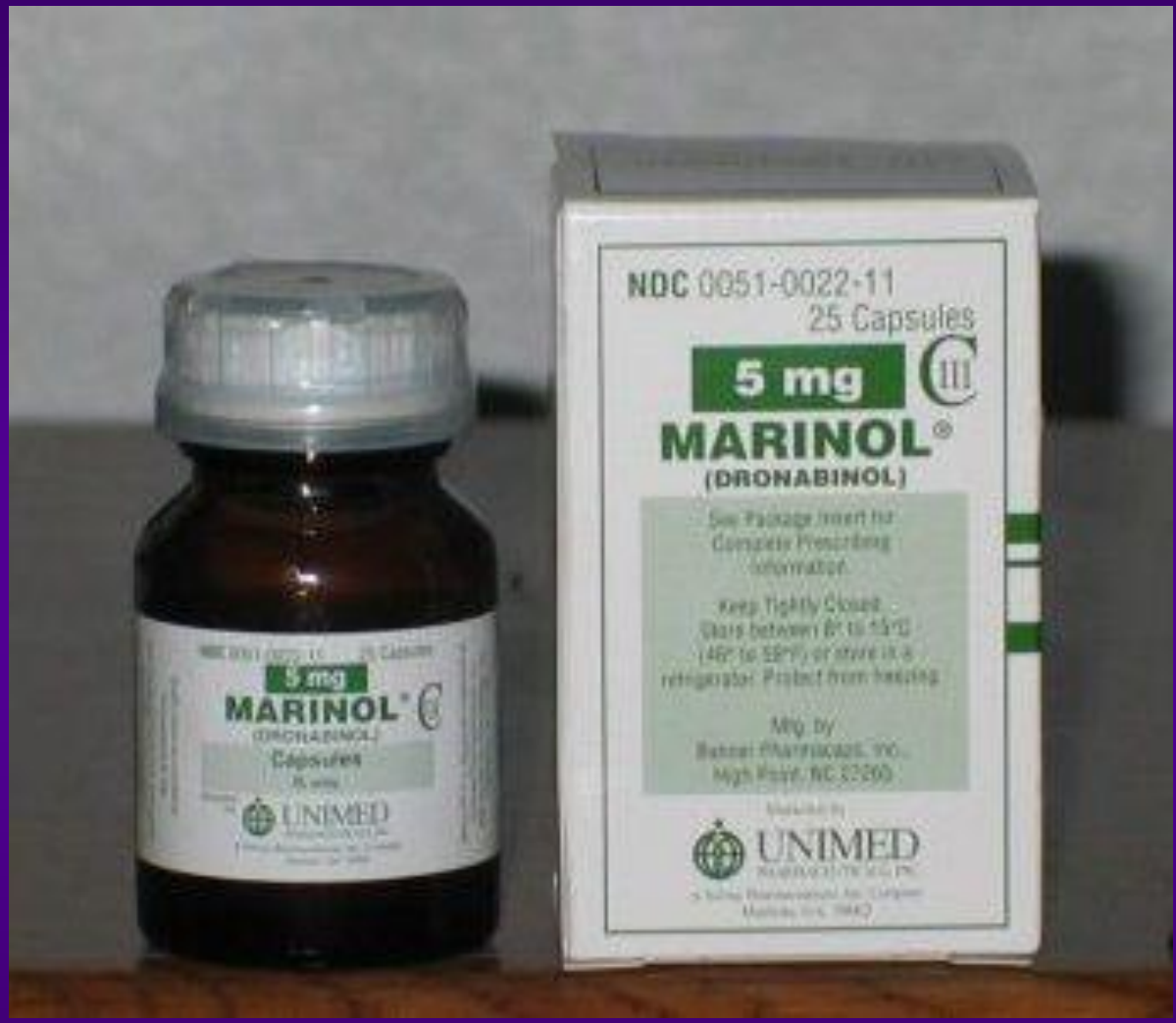
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Capsules
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NDC 0051-0022-11
25 Capsules
5 mg
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MARINOL®
(DRONABINOL)
Keep Tightly Closed
Mfg. by
UNIMED


No. 1000 581
COMPRESSED
TABLETS
MIGRAINE
No. 3
ACETPHENETIDIN U. S. P.
(Acetanilid derivative)
2 1-2 gr.
EXTR. CANNABIS 1-16 gr.
Extr. Hyoscyamus 1-8 gr.
Camphor monobrom. 1-2 gr.
Caffeine 1-4 gr.
Dose, 1 to 2 Tablets
SHARP & DOHME
BALTIMORE

Point to remember

- Very few good studies
- Results are not impressive
- Multiple difficulties for clinical research
- Initial planning will help to create good studies
- Always remember what is the alternative (Opioids, Anti-depressant, Anti-convulsant, Benzodiazepines)


Thank you
Z.KLEIN
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Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial.

Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH.

Neuropsychopharmacology 2009;34(3):672-680.

Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. Cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception. We conducted a clinical trial to assess the impact of smoked cannabis on neuropathic pain in HIV. This was a phase II, double-blind, placebo-controlled, crossover trial of analgesia with smoked cannabis in HIV-associated distal sensory predominant polyneuropathy (DSPN). Eligible subjects had neuropathic pain refractory to at least two previous analgesic classes; they continued on their prestudy analgesic regimens throughout the trial. Regulatory considerations dictated that subjects smoke under direct observation in a hospital setting. Treatments were placebo and active cannabis ranging in potency between 1 and 8% Delta-9-tetrahydrocannabinol, four times daily for 5 consecutive days during each of 2 treatment weeks, separated by a 2-week washout. The primary outcome was change in pain intensity as measured by the Descriptor Differential Scale (DDS) from a pretreatment baseline to the end of each treatment week. Secondary measures included assessments of mood and daily functioning. Of 127 volunteers screened, 34 eligible subjects enrolled and 28 completed both cannabis and placebo treatments. Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size=0.60; p=0.016). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%CI 0.28, 0.65) and 0.18 (0.03, 0.32). Mood and daily functioning improved to a similar extent during both treatment periods. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities. Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV DSPN.

CMAJ RESEARCH

Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Methods: Adults with post-traumatic or postsurgical neuropathic pain were randomly assigned to receive cannabis at four potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) over four 14-day periods in a crossover trial. Participants inhaled a single 25-mg dose through a pipe three times daily for the first five days in each cycle, followed by a nine-day washout period. Daily average pain intensity was measured using an 11-point numeric rating scale. We recorded effects on mood, sleep and quality of life, as well as adverse events.

Results: We recruited 23 participants (mean age 45.4 [standard deviation 12.3] years, 12 women [52%]), of whom 21 completed the trial. The average daily pain intensity, measured on the 11-point numeric rating scale, was lower on the prespecified primary contrast of 9.4% v. 0% tetrahydrocannabinol (5.4 v. 6.1, respectively; difference = 0.7, 95% confidence interval [CI] 0.02–1.4). Preparations with intermediate potency yielded intermediate but nonsignificant degrees of relief. Participants receiving 9.4% tetrahydrocannabinol reported improved ability to fall asleep (easier, $p = 0.001$; faster, $p < 0.001$; more drowsy, $p = 0.003$) and improved quality of sleep (less wakefulness, $p = 0.01$) relative to 0% tetrahydrocannabinol. We found no differences in mood or quality of life. The most common drug-related adverse events during the period when participants received 9.4% tetrahydrocannabinol were headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough.

Conclusion: A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated

A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain.

Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S.

J Pain. 2008 Apr 8 [Epub ahead of print]

The Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the National Institute for Drug Abuse (NIDA) report that no sound scientific studies support the medicinal use of cannabis. Despite this lack of scientific validation, many patients routinely use "medical marijuana," and in many cases this use is for pain related to nerve injury. We conducted a double-blinded, placebo-controlled, crossover study evaluating the analgesic efficacy of smoking cannabis for neuropathic pain. Thirty-eight patients with central and peripheral neuropathic pain underwent a standardized procedure for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis. In addition to the primary outcome of pain intensity, secondary outcome measures included evoked pain using heat-pain threshold, sensitivity to light touch, psychoactive side effects, and neuropsychological performance. A mixed linear model demonstrated an analgesic response to smoking cannabis. No effect on evoked pain was seen. Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication.

Randomised Placebo Controlled Double Blind Clinical Trial of Cannabis Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy: Depression is a Major Confounding Factor

Selvarajah D, Gandhi R, Emery CJ, Tesfaye S.

Diabetes Care. 2010 Jan;33(1):128-30.

Objective- To assess the efficacy of Sativex, a cannabis based medicinal extract, as adjuvant treatment in painful-DPN. Research design and methods- In this randomized controlled trial, 30 subjects with painful-DPN received daily Sativex or placebo. Primary outcome measure was change in mean daily pain scores and secondary outcome measures included quality of life assessments. Results- There was significant improvement in pain scores in both groups but mean change between groups was not significant. There were no significant differences in secondary outcome measures. Patients with depression had significantly greater baseline pain scores that improved regardless of intervention. Conclusion- This first ever, trial assessing the efficacy of cannabis has shown it to be no more efficacious than placebo in painful-DPN. Depression was a major confounder and may have important implications for future painful-DPN trials.

Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with secondary progressive multiple sclerosis.

Conte A, Bettolo CM, Onesti E, Frasca V, Iacovelli E, Gilio F, Giacomelli E, Gabriele M, Aragona M, Tomassini V, Pantano P, Pozzilli C, Inghilleri M.

Eur J Pain. 2009 May;13(5):472-7.

Although clinical studies show that cannabinoids improve central pain in patients with multiple sclerosis (MS) neurophysiological studies are lacking to investigate whether they also suppress these patients' electrophysiological responses to noxious stimulation. The flexion reflex (FR) in humans is a widely used technique for assessing the pain threshold and for studying spinal and supraspinal pain pathways and the neurotransmitter system involved in pain control. In a randomized, double-blind, placebo-controlled, cross-over study we investigated cannabinoid-induced changes in RIII reflex variables (threshold, latency and area) in a group of 18 patients with secondary progressive MS. To investigate whether cannabinoids act indirectly on the nociceptive reflex by modulating lower motoneuron excitability we also evaluated the H-reflex size after tibial nerve stimulation and calculated the H wave/M wave (H/M) ratio. Of the 18 patients recruited and randomized 17 completed the study. After patients used a commercial delta-9-tetrahydrocannabinol (THC) and cannabidiol mixture as an oromucosal spray the RIII reflex threshold increased and RIII reflex area decreased. The visual analogue scale score for pain also decreased, though not significantly. Conversely, the H/M ratio measured before patients received cannabinoids remained unchanged after therapy. In conclusion, the cannabinoid-induced changes in the RIII reflex threshold and area in patients with MS provide objective neurophysiological evidence that cannabinoids modulate the nociceptive system in patients with MS.

Conclusions: Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated

Three Cannabis Based Medicinal Extracts (CBMEs) for sublingual use for patients with chronic, mainly neuropathic, pain and associated symptoms to explore efficacy, tolerability, safety and dosages. Three CBMEs were given over a 12-week period. After an initial open-label period, the CBMEs were used in a randomised, double-blind, placebo controlled, crossover trial.

Extracts which contained THC proved most effective in symptom control

Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review

Fiona A Campbell, Martin R Tramèr, Dawn Carroll, D John M Reynolds, R Andrew Moore, Henry J McQuay

Chronic non-malignant pain									
Holdcroft et al[25]	n=1; n of 1 crossover design; pain: abdominal (Mediterranean fever); follow up 6 weeks	1, 2, 0	THC 10 mg x 5 capsules/day; placebo x 5 capsules/day (each treatment 1 week)	No data	VAS (ranges): THC 4.8-6.2 mm; placebo 5.5-6.1 mm; NS	Daily morphine consumption less in THC group (P<0.001)		Nausea and vomiting throughout study;dysphoria and irritability associated with placebo weeks	Experienced cannabis user able to identify THC capsules for first 4 weeks of trial
Maurer et al[26]	n=1; n of 1 crossover design; pain: spinal cord pathology; follow up 5 months	1, 2, 0	THC 5 mg x 18; codeine 50 mg x 18; placebo x 18	No data	VAS (50 mm scale): THC 25.6 mm; codeine 19.7 mm; placebo 34.3 mm; P<0.05 for THC and codeine *v* placebo	THC had only antispasticity effect		THC and codeine better than placebo for mood, sleep, concentration, control of micturition, global effect; no altered state of consciousness	
Postoperative pain									
Jain et al (phase 1)[27]	n=36 (36 analysed); parallel group design; pain: postoperative or trauma (moderate to severe pain); follow up 6 hours	1, 1, 1	Intramuscular: levonantradol 1.5 mg x 1; levonantradol 2.0 mg x 1; placebo x 1	AUDC: P<0.05 for levonantradol *v* placebo at each dose	AUDC: P<0.05 for levonantradol *v* placebo at each dose		No of patients with reactions: levonantradol 23/40; placebo 2/16	Drowsiness common Dry mouth, dizziness, and dysphoria uncommon Levonantradol: increased heart rate and reduced blood pressure (no dose response)	
Jain et al (phase 2)[27]	n=36 (36 analysed); parallel group design; pain: postoperative or trauma (moderate baseline pain); follow up 6 hours	1, 1, 1	Intramuscular: levonantradol 2.5 mg x 1; levonantradol 3.0 mg x 1; placebo x 1	AUDC: P<0.05 for levonantradol *v* placebo at each dose	AUDC: P<0.05 for levonantradol *v* placebo at each dose				

BPP=benzopyranoperidine;THC=9-delta-tetrahydrocannabinol; NIB=nitrogen analogue THC.
AUDC=areas under the difference curves (sum of change from baseline to six hours for pain intensity, pain relief, and pain analgesic scores).
SPID=summed pain intensity difference.
VAS=visual analogue scale.

Analysis of nine randomised controlled trials of effectiveness of cannabinoids for three types of pain (cancer pain, chronic non-malignant pain, and postoperative pain)

Trial	Study chacterisitcs	Quality score (randomisation, blinding, withdrawals)	Intervention (oral unless indicated otherwise)	Efficacy data: Pain relief (total pain relief or AUDC)	Efficacy data: Pain intensity (SPID orVAS)	Efficacy data: Other	Adverse drug reactions: Quantitatively	Adverse drug reactions: Qualitatively	Comments
Cancer pain									
Jochimsen et al[21]	n=37 (35 analysed); crossover design; pain: cancer (moderate baseline pain); follow up 6 hours	1, 2, 0	BPP 2 mg x 1; BPP 4 mg x 1; codeine 60 mg x 1; codeine 120 mg x 1; placebo x 1	Complete: BPP 2 mg 2/35; BPP 4 mg 3/35; codeine 60 mg 9/35; codeine 120 mg 8/35; placebo 4/35	Reduced: BPP 2 mg 19/35; BPP 4 mg 20/35; codeine 60 mg 25/35; codeine 120 mg 31/35; placebo 25/35			11 item self assessment scale showed no difference in psychotomimetic effect. Sedation for both doses of BPP similar to both doses of codeine. No difference in blood pressure, heart rate, psychiatric interview	37 patients entered, 35 completed (no reason given for 2 who did not complete); analgesic effect of codeine 120 mg better than placebo, BPP 4 mg worse than placebo; adverse effects not significantly different
Noyes et al[22]	n=10 (9 analysed); crossover design; pain: cancer (moderate baseline pain); follow up 6 hours	1, 2, 0	THC 5 mg x 1; THC 10 mg x 1; THC 15 mg x 1; THC 20 mg x 1; placebo x 1	Total (mean±SE): THC 5 mg 4.7±0.95; THC 10 mg 4.4±0.98; THC 15 mg 5.8±0.84; THC 20 mg 10.8±1.19; placebo 5.1±1.65;	SPID (mean±SE): THC 5 mg 2.6±0.53; THC 10 mg 1.4±0.42; THC 15 mg 3.6±0.65; THC 20 mg 4.6±0.66; placebo 0.9±0.3	Progressive pain relief with increasing doses of THC (P<0.001)	No of reactions per 10 patients: THC 5 mg 37; THC 10 mg 47; THC 15 mg 64; THC 20 mg 70; placebo 16	Progressive sedation and mental clouding (THC 20 mg caused heavy sedation in all patients); reduced blood pressure and heart rate; euphoria in 2 patients receiving THC 15 mg and 20 mg, 1 of whom was the only experienced marijuana user	Dose response for analgesia and adverse effects with THC
Noyes et al[23]	n=36 (34 analysed); crossover design; pain: cancer (moderate baseline pain); follow up 7 hours	1, 2, 0	THC 10 mg x 1; THC 20 mg x 1; codeine 60 mg x 1; codeine 120 mg x 1; placebo x 1	Total (mean±SE): THC 10 mg 9.8±1.40; THC 20 mg 12.9±1.46; codeine 60 mg 9.4±1.38; codeine 120 mg 12.2±1.57; placebo 6.8±0.95; P<0.05=THC 20 mg and codeine 120 mg *v* placebo	SPID (mean±SE): THC 10 mg 2.9±0.62; THC 20 mg 4.7±0.65; codeine 60 mg 3.6±0.75; codeine 120 mg 4.3±0.78; placebo 1.9±0.44; P<0.05 for THC 20 mg and codeine 120 mg *v* placebo	Analgesic effect of THC in 5 hours, codeine in 3 hours	No of reactions per 34 patients: THC 10 mg 186; THC 20 mg 259; codeine 60 mg 120; codeine 120 mg 13; placebo 92. Withdrawal owing to reactions: THC 2; codeine or placebo 0	Reduced blood pressure with THC	THC 20 mg highly sedating and produced mental effects prohibiting its use. THC 10 mg was well tolerated and somewhat sedating, but only equipotent to codeine 60 mg
Staquet et al (study 1)[24]	n=30 (26 analysed); crossover design; pain: cancer (moderate baseline pain); follow up 6 hours	1, 2, 1	NIB 4 mg x 1; codeine 50 mg x 1; placebo x 1	No data	SPID (mean±SE): NIB 4.72±3.33; codeine 4.79±3.19; placebo 2.15±2.56; P<0.05 for NIB and codeine *v* placebo		Drowsiness (% of patients): NIB 40%; codeine 44%; placebo 21%	4 withdrawals unrelated to study drug	
Staquet et al (study 2)[24]	n=15 (15 analysed); crossover design; pain: cancer (moderate baseline pain);	1, 2, 1	NIB 4 mg x 1; secobarbital 50 mg x 1; placebo x 1	No data	SPID (mean±SE): NIB 4.40±2.06; secobarbital 2.13±1.77; placebo 1.87±1.30; P<0.05 for NIB *v*		Drowsiness: (% of patients): NIB 40%; secobarbital 33%; placebo 21%		Secobarbital did not reduce pain intensity more than placebo, indicating that hypnotic properties do not imply pain

Conclusion

The best that can be achieved with single dose cannabis in nociceptive pain is analgesia equivalent to single dose codeine 60 mg, which rates poorly on relative efficacy compared with non-steroidal anti-inflammatory drugs or simple analgesics. Increasing the cannabinoid dose to increase the analgesia will increase adverse effects. More intriguing perhaps than these relatively negative analgesic results in nociceptive pain are the suggestions of efficacy in spasticity and in neuropathic pain, where the therapeutic need is greater than in postoperative pain.