Marijuana and Pain Control

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Disclaimers

NONE

Objectives

- Understand the Historical context of Marijuana
- THC vs CBD
- Mechanism of Action
- Medical roles for Cannabinoids

Marijuana
Historical Usage

- 2900 BC – First modern reference
  - Emperor Fu Hsi mentions it as a popular medicine due to it having yin (negative feminine)and yang (positive masculine)

- 1500 BC – Earliest written record in medicine
  - Listing in Chinese Pharmacopeia

Marijuana

- 70 AD – Roman medical text cited
  - Cannabis to treat ear ache and to suppress sexual longing
- 1850 – Cannabis added to the U.S. Pharmacopeia Standards
- 1889 – Published in *The Lancet*
  - Use in opioid withdrawal

Marijuana

THE USE OF INDIAN HEMP IN THE TREATMENT OF CHRONIC CHLORAL AND CHRONIC OPIUM POISONING.

Edward A. Birch, M.D., M.R.C.P. (HONORARY MEMBER OF THE CALCUTTA MEDICAL SOCIETY ; PHYSICIAN TO THE GENERAL HOSPITAL, CALCUTTA.)

Volume 133, Issue 3422, 30 March 1889

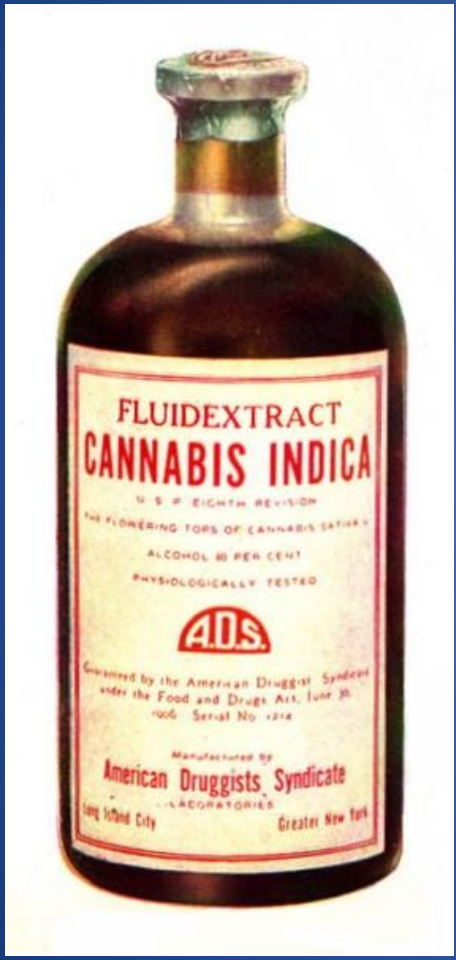
Legal Marijuana in the U.S.

- Only in the late 19th century did the use of Marijuana begin as a popular ingredient in many medical products sold openly in pharmacies
- It was NOT illegal to grow or possess!!

Marijuana in the U.S.

- 1890s – Smoking of hashish becomes a fad in France and crosses over to the U.S.

- 1906 – Pure Food Act requires labeling of any cannabis containing product over the counter


FLUIDEXTRACT
CANNABIS INDICA
U. S. P. EIGHTH REVISION
THE FLOWERING TOPS OF CANNABIS SATIVA L.
ALCOHOL 80 PER CENT
PHYSIOLOGICALLY TESTED
ADS.
Guaranteed by the American Druggist Syndicate under the Food and Drugs Act, June 30, 1906. Serial No. 1214
Manufactured by
American Druggists Syndicate
LABORATORIES
Long Island City
Greater New York


ONE NIGHT
TRADE MARK
COUGH SYRUP
EACH OUNCE CONTAINS
ALCOHOL, (less than 1%) 4¾m.
CANNABIS INDICA, F.E. 4½m.
CHLOROFORM, 2½m.
MORPHIA, SULPH. ⅛gr.
SKILLFULLY COMBINED WITH A NUMBER OF OTHER INGREDIENTS
DIRECTIONS

Marijuana and Pain Control

THC vs CBD


SATIVA
INDICA
RUDERALIS
SATIVA
CBD << THC
INDICA
CBD >> THC
MiniHemp

Marijuana and Pain Control

- There are over 483 know components of which the main psychoactive is

  Delta-Tetrahydrocannabinol (THC)
- There are also 150 other cannabinoids present
- Phyto-Cannabinoids up to 40% of the active agents

TERPENES

- Oily compounds secreted in marijuana plants glandular trichomes, volatile/aromatic
- Ubiquitous throughout the natural world
- 20K have been identified in plant world, marijuana found to have over 200 types
- Similar to cannabinoids, except for repeating aromatic 5 carbon ring called isoprene

TERPENES

- **Alpha-pinene** (essential pine oil), the most common terpene in the plant world and one often found in cannabis, is a bronchodilator potentially helpful for asthmatics. Pinene also promotes alertness and memory retention by inhibiting the metabolic breakdown of acetylcholinesterase, a neurotransmitter in the brain that stimulates these cognitive effects.
- **Myrcene**, another terpene present in numerous cannabis varietals, is a sedative, a muscle relaxant, a hypnotic, an analgesic (painkiller) and an anti-inflammatory compound. This musky terpene contributes mightily to the infamous "couch-lock" experience, Russo maintains.
- **Limonene**, a major terpene in citrus as well as in cannabis, has been used clinically to dissolve gallstones, improve mood and relieve heartburn and gastrointestinal reflux. Limonene, an anticonvulsant, has been shown to destroy breast-cancer cells in lab experiments, and its powerful antimicrobial action can kill pathogenic bacteria. (Lemon Kush, anyone?)
- **Linalool**, a terpenoid prominent in lavender as well as in some cannabis strains, is an anxiolytic compound that counters anxiety and mediates stress. In addition, linalool is a strong anticonvulsant, and it also amplifies serotonin-receptor transmission, conferring an antidepressant effect. Applied topically, linalool can heal acne and skin burns without scarring.
- **Beta-caryophyllene** is a sesquiterpene found in the essential oils of black pepper, oregano and other edible herbs, as well as in cannabis and many green, leafy vegetables. It is gastro-protective, good for treating certain ulcers, and shows great promise as a therapeutic compound for inflammatory conditions and autoimmune disorders because of its ability to bind directly to the peripheral cannabinoid receptor known as CB2.

TERPENES

- Both Terpenes and CBD are know to temper the psychoactive effects and anxiety effects of THC
- help to create the “entourage” effect, magnifies the therapeutic effects of the individual components

Marijuana and Pain Control

- High lipid solubility thus rapid CNS levels and also long ½ life in the body

- Urine drug screens can be positive for up to 30 days for THC
- Urine screens do NOT check for CBD!

Definitions

- Cannabinoid-compound that act at cannabinoid receptors
- The main receptors are CB1 and CB2
- However primary secondary receptors are TRPV1, GPR 55, GPR3 and GPR19

Definitions

- G-Coupled proteins when activated decrease Adenyl Cylase in a dose dependent way thus alter signaling
- Opioid receptors are also G-reactive
- When activated centrally they will increase dopamine release which causes its psychotropic affects

Cannabinoids

- CB1-

  Highly expressed in the nervous system receptors in the Hippocampus, Amygdala, Basal Gangli, Cerebellum, Nucleus Accumbens, and Cortex

Cannabinoids

- CB2B

  Spleen, Intestines, Thymus, Testes,

  Leuckocytes, Macrophages
- CB2A

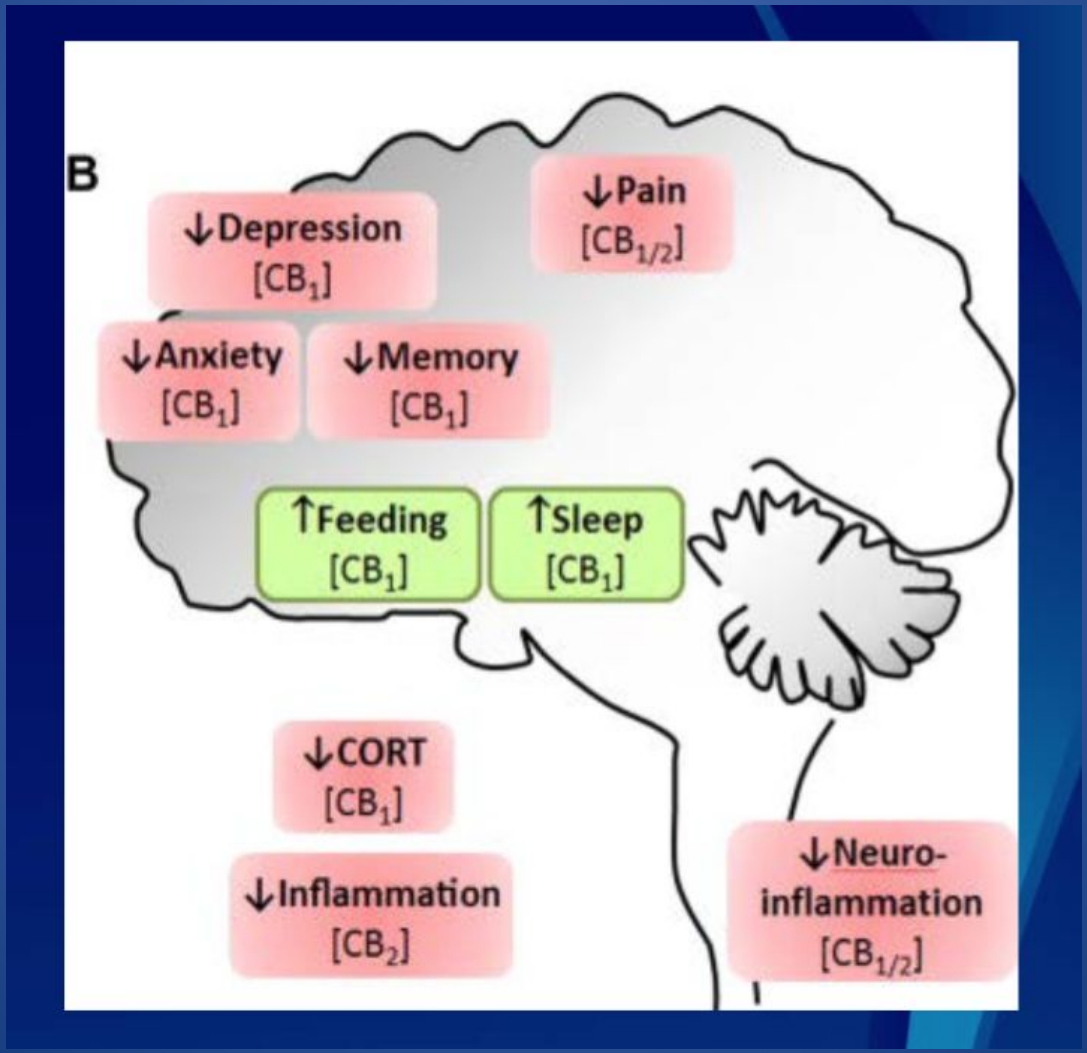
  Brain, Spinal Cord, Glial Cells

Cannabinoid Receptors

- CB-1 up regulates at gabaneric (inhibitory) and down regulates at glutaminergic (excitatory)

- CB2 primary immune function

Cannabinoid Receptors



Effects on Cannabinoid Receptors

- DECREASE

  IGM, IGG, Macrophage activity, Cytokine,

  Killer Cells, can cause decrease in total

  Immune function,
- Inhibit proliferation of Delta TNF alpha, and T Cells

Endocannabinoids

- **Anandamide** and **2-Arachidonoyl-glycerol (2-AG)** are produced in injured tissues :
  - ✓ **Anandamide** is a CB1 agonist and CB2 partial agonist
  - ✓ **2-AG** is a CB1 et CB2 agonist

Endocannabinoids

- Anandamide also binds to TRPV1 receptors and activates channels in the CNS and peripheral nerves
- Partial agonist CB1 and CB2
- Inactivated by fatty acid amide hydrolase (FAAH)

TRPV1 Receptors

- Transient Receptor Potential Vanilloid -1
- High levels in CNS
- Pre-Synaptic
- Activation actually leads to painful burning sensation
- Involved in temperature regulation
- Capsaicin – agonist, prolonged use desensitize
- Anandamide/THC-CBD – activates partial

TRPV1 Receptors

- Prolonged activity leads to decrease signaling thus decrease release of inflammatory molecules such as Prostoglandin/Bradykinen
- Thus chronic use of Cannabinoids would affect pain relief

Endocannabinoids

- 2AG (2-Arachidonylglyceral)
- full agonist at CB1 and CB2
- Ca dependent channels
- Inactivated by monoacylglyerol lipase (MAGL)

Animal Studies

- FAAH knock out mice have increased levels of Anandamide and show reduced pain sensation in hot plate, formalin and tail flick tests
- Local administration of MAGL inhibitors into rat hind paws increases local levels of AG-2 with attenuation of formalin test
- FAAH inhibitor decreases allodynia and hyperalgesia in neuropathic mice model

THC

- Phyto or Synthetic
- The primary psychoactive cannabinoid in cannibus, its metabolites are the primary ones assayed in drug tests
- Binds equally to CB1 and CB 2 but the majority of its effects are CB1 in the brain

CBD

- Not psychoactive
- Thought to protect against the psychoactive effects of THC
- Also acts as a 5Ht receptor agonist
- Low affinity to CB1 and CB2 but can act as an antagonist of CB1 and CB2 maybe antagonist to GPR 55
- Possible inverse agonist at GPR 3,6,12

CBD

- Evidence that CBD alters the absorption of anandamide
- CBD binds to glial cells causing decreased production of cytokine
- (glial cell, specifically microglia, up regulation seen in injury/chronic pain states)

CBD

- CBD extensive metabolization by the CYP3A4 system only @ 6% bio available, ½ life 1-2 days
- Must be used chronically not for acute pain
- CBD inhibitor of CYP2D6-tramadol
  CYP2C9-coumadin

Vegetal

Sativex (Nabiximols)

- Formulated extract of the cannabis sativa plant
- Oromucosal spray
- THC and cannabidiol in a 1:1 ratio
- Contains specific minor cannabinoids
- Treatment of spasticity due to MS

Synthetic

Dronabinol (Marinol)

- Synthetic THC (98%)
- CB1 and CB2 receptor agonist
- Antiemetic for chemotherapy and an appetite stimulant for persons with AIDS (FDA approved since 1985)
- Bioavailability is 10%.
- Central nervous system toxicity !

Synthetic

Nabilone (Cesamet)

- Synthetic analogue of THC
- CB1 and CB2 receptor agonist
- Antiemetic in chemotherapy patients (FDA approved).
- Unapproved use is spasticity-related pain or Parkinson

Potential Benefits of Cannabinoids

- Antiemetic[1] – Marinol is FDA-approved (Schedule III) for use in post-chemotherapy nausea/vomiting
- Anorexia – Marinol is FDA-approved for this use in AIDS-induced anorexia in US
- Anti-spasticity agent[2]
- Anticonvulsant[3] – Focus on CBD effects
- Neuroprotective
  - Being studied in Alzheimer's[4] because preclinical models show CB1/2 activation leads to reduction in beta-amyloid
  - Retrospective study of patients admitted with severe TBI showed significant reduction in death in those who had a positive drug screen for THC[5]
- Anti-tumor effects[6]

AIDS, acquired immune deficiency syndrome; CB, cannabinoid receptor; CBD, cannabidiol; FDA, Food and Drug Administration; TBI, traumatic brain injury; THC, tetrahydrocannabinol

1. Sharkey K, et al. Eur J Pharm. 2014; 722:134-46. 2. Koppel, et al. Neurology. 2014;82:1556-63. 3. Devinsky O. Epilepsia;2014:55:791-802.
4. Aso E, et. al. Front Pharmacol. 2014;5:37. 5. Nguyen BN. Am Surg. 2014;80:979-83. 6. Cridge B, Rosengren RJ. Cancer Manag Res. 2013;5:301-13.

Potential Benefits

- So far the best evidence is for treatment of central or neuropathic pain
- Little evidence that they help in nociceptive or inflammatory type pain
- Cannabinoids can exert analgesic effects in the periphery (mainly anti-inflammatory) and in the CNS (dissociative effect)

Side Effects Cannabis

- Addiction!! There is a Cannibus Use Disorder (CUD), 2-5% of worlds population use Cannabis
- World Drug Report 2017, those who sought treatment for addiction, 39% Cannabis, 33% Opioids, 10% Cocaine
- 9% of all cannabis users, male >>female, young age, high remission rate 17.3%

Side Effects Cannabis
Acute

- Increased CV effects, tachycardia, vasodilatation, primarily in the elderly myocardial O2 demand, MI, arrhythmia, sudden cardiac death
- Sleepiness, fatigue, weakness, dizzyness, dry mouth
- Low blood sugar
- Increased appetite

Side Effects Cannabis Chronic

- Smoking increased risk of respiratory issues
- Increased risk of testicular cancer
- Decrease efficacy of immune therapy from 38% response to 16% in cancer treatment
- Long term use can cause structural changes in the amygdala, hippocampus
- Change in volume, shape gray matter density

Cannabis Side Effects Societal

- European Study
- Eva Hoch, Ludwig Maximilian University,Germany
- In teens regular cannabis use leads to lower education, significant association with High School drop out, decreased Higher degrees, greater welfare dependence, increased risk of depression, Bipolar Symptoms, these are dose dependent

Marijuana Pain Control

- Abrams, et al. *Cannabinoid-opioid interaction in chronic pain*

  Clin Pharmacol Ther 2011;90:844-51

- 21 patients with chronic pain due to arthritis, neuropathy, cancer, MS
- Patients using either Morphine ER 62mg q12 or oxycodone 53mg q12 (average doses)
- Vaporized cannabis x5 days

Marijuana Pain Control

Abrams, et al.

- Pain significantly decreased 27% (avg)
- No change in area under curve for morphine or oxycodone usage

Marijuana Pain Control

APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE

Review Article

A selective review of medical cannabis in cancer pain management

Alexia Blake[1], Bo Angela Wan[2], Leila Malek[2], Carlo DeAngelis[2,3], Patrick Diaz[2], Nicholas Lao[1], Edward Chow[2], Shannon O'Hearn[1]

[1]MedReleaf, Markham, Ontario, Canada; [2]Odette Cancer Centre, Sunnybrook Health Sciences Centre, [3]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Contributions: (I) Conception and design: A Blake, E Chow, S O'Hearn; (II) Administrative support: BA Wan, L Malek, P Diaz; (III) Provision of study materials or patients: N Lao; (IV) Collection and assembly of data: A Blake, BA Wan, L Malek, S O'Hearn; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Blake et al

- Reviewed literature from 1975-2017
- Found 5 clinical studies of THC or CBD on Cancer Pain

Blake et al

- Treatments were either
  - THC Oil capsules
  - THC/CBD oromucosal spray (Nabiximols)
  - THC oromucosal spray

Blake et al

- Dosing wide variability, from 2.4-43.2 mg/day of THC and 0-40 mg/day of CBD
- One study reported improved relief with combo of THC/CBD, both at lower doses
- Authors felt that there was evidence suggesting medical cannabis reduces chronic or neuropathic pain in advanced cancer patients

Journal of Drug and Alcohol Dependency

Experience of adjunctive cannabis use for chronic non-cancer pain: Findings from the Pain and Opioids IN Treatment (POINT) study

Louisa Degenhardt[a,b,*], Nicholas Lintzeris[c,d], Gabrielle Campbell[a], Raimondo Bruno[a,e], Milton Cohen[f], Michael Farrell[a], Wayne D. Hall[g,h]

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ABSTRACT

Background: There is increasing debate about cannabis use for medical purposes, including for symptomatic treatment of chronic pain. We investigated patterns and correlates of cannabis use in a large community sample of people who had been prescribed opioids for chronic non-cancer pain.

Methods: The POINT study included 1514 people in Australia who had been prescribed pharmaceutical opioids for chronic non-cancer pain. Data on cannabis use, ICD-10 cannabis use disorder and cannabis use for pain were collected. We explored associations between demographic, pain and other patient characteristics and cannabis use for pain.

Results: One in six (16%) had used cannabis for pain relief, 6% in the previous month. A quarter reported that they would use it for pain relief if they had access. Those using cannabis for pain on average were younger, reported greater pain severity, greater interference from and poorer coping with pain, and more days out of role in the past year. They had been prescribed opioids for longer, were on higher opioid doses, and were more likely to be non-adherent with their opioid use. Those using cannabis for pain had higher pain interference after controlling for reported pain severity. Almost half (43%) of the sample had ever used cannabis for recreational purposes, and 12% of the entire cohort met criteria for an ICD-10 cannabis use disorder.

Conclusions: Cannabis use for pain relief purposes appears common among people living with chronic non-cancer pain, and users report greater pain relief in combination with opioids than when opioids are used alone.

Marijuana Pain Control

Whiting PF, et al. *Cannabinoids for Medical Use: A Systemic Review and Meta-Analysis*. JAMA 2015;13(24):2456-73

- Moderate quality evidence to support use of cannabinoids for Tx of chronic pain spasticity due to MS
- Low quality evidence associated with improvement in:
  - Nausea/vomiting due to chemotx
  - weight gain in HIV pts
  - sleep disorders
  - Tourette's

Marijuana Pain
October 2017

REVIEW ARTICLE

Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts

Kevin P. Hill[1,2], Matthew D. Palastro[3]

1 Division of Addiction Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States
2 Harvard Medical School, Boston, Massachusetts, United States
3 New York Medical College, Valhalla, New York, United States

Marijuana Pain
October 2017

TABLE 1 Indications for medical cannabis and the quality of randomized placebo--controlled studies showing its efficacy

Indication	Quality of evidence
Chronic and neuropathic pain	Moderate to high[1-7]
Spasticity associated with multiple sclerosis	Moderate to high[8-22]
Seizure disorders	Moderate to high[23-31]
Gastrointestinal disorders	Moderate[32-39]
HIV and acquired immunodeficiency syndrome	Moderate[40-51]
Glaucoma	Low[52-56]
Posttraumatic stress disorder	Low[57-65]
Parkinson disease	Low[66-72]

Chronic Pain

EJP European Journal of Pain

EFIC

ORIGINAL ARTICLE | Full Access

Medical cannabis treatment for chronic pain: Outcomes and prediction of response

Joshua Aviram, Dorit Pud, Tamar Gershoni, Bareket Schiff-Keren, Miriam Ogintz, Simon Vulfsons, Tamar Yashar, Haim-Moshe Adahan, Silviu Brill, Howard Amital, Itay Goor-Aryeh, ... See all authors

First published: 16 October 2020 | https://doi-org.proxy.libraries.rutgers.edu/10.1002/ejp.1675 |
Citations: 2

Aviram et. Al.

- 1,045 patients licensed to use medical cannabis were enrolled
- Observational study, multiple pain issues
- Followed up 1,3,6,9 and 12 months

Aviram et. al

- Found 15-20% reduction of pain at one year with all pain conditions
- Found a steep reduction in overall MME use of analgesics
- Predictors of success; normal to longer sleep duration, lower BMI, lower depression score and a diagnosis *other then Neuropathic Pain.*

Marijuana/Opioids

- M. Olsen, M. Wall et al
  Cannabis Use and Risk of Prescription Opioid Disorder in the United States, American
  of Psychiatry, Sept. 2017

Author concluded that cannabis use appears to *Increase* rather then *Decrease* the risk of developing non medical prescription opioid use and opioid use disorder

Marijuana/Opioids

Harm Reduct J. 2019 Jan 28;16(1):9. doi: 10.1186/s12954-019-0278-6.

Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients.

Lucas P[1,2,3], Baron EP[4], Jikomes N[5].

⊕ Author information

Abstract

BACKGROUND: A 239-question cross-sectional survey was sent out via email in January 2017 to gather comprehensive information on cannabis use from Canadian medical cannabis patients registered with a federally authorized licensed cannabis producer, resulting in 2032 complete surveys.

METHODS: The survey gathered detailed demographic data and comprehensive information on patient patterns of medical cannabis use, including questions assessing the self-reported impact of cannabis on the use of prescription drugs, illicit substances, alcohol, and tobacco.

RESULTS: Participants were 62.6% male (n = 1271) and 91% Caucasian (n = 1839). The mean age was 40 years old, and pain and mental health conditions accounted for 83.7% of all respondents (n = 1700). Then, 74.6% of respondents reported daily cannabis use (n = 1515) and mean amount used per day was 1.5 g. The most commonly cited substitution was for prescription drugs (69.1%, n = 953), followed by alcohol (44.5%, n = 515), tobacco (31.1%, n = 406), and illicit substances (26.6%, n = 136). Opioid medications accounted for 35.3% of all prescription drug substitution (n = 610), followed by antidepressants (21.5%, n = 371). Of the 610 mentions of specific opioid medications, patients report total cessation of use of 59.3% (n = 362).

CONCLUSIONS: This study offers a unique perspective by focusing on the use of a standardized, government-regulated source of medical cannabis by patients registered in Canada's federal medical cannabis program. The findings provide a granular view of patient patterns of medical cannabis use, and the subsequent self-reported impacts on the use of opioids, alcohol, and other substances, adding to a growing body of academic research suggesting that increased regulated access to medical and recreational cannabis can result in a reduction in the use of and subsequent harms associated with opioids, alcohol, tobacco, and other substances.

Alabama Medical Cannabis

- Medical Cannabis Act 2021-450 was signed into law by Governor Kay Ivey on May 17, 2021
- Known as the Darren Wesley “Ato”Hall Compassion Act
- Named after the son of State Representative Laura Hall who’s son died of AIDS at age 25

Alabama Medical Cannibus

- Medical Cannabis may NOT be used by smoking or vaping, or consuming food products such as cookies or candies

Alabama Medical Cannibis

- Approved Uses
- 15 Categories of Conditions/Symptoms

Alabama Medical Cannibis

Autism; cancer-related weight loss, or chronic pain; Crohn's; depression; epilepsy or condition causing seizures; HIV/AIDS-related nausea or weight loss; panic disorder; Parkinson's; persistent nausea not related to pregnancy; PTSD; sickle cell; spasticity associated with diseases including ALS and multiple sclerosis, and spinal cord injuries; terminal illnesses; Tourette's; chronic pain for which conventional therapies and opiates should not be used or are ineffective.

Alabama Medical Cannibus

- Unfortunately, Patrick Moody deputy Commissioner of the Alabama Department of Agriculture has recently stated that he didn't expect licenses for medical marijuana growers could be issued before 9/1/22
- Once licenses are issued then growers can start to cultivate (take @ 3-4 months)
- So really not available until 2023!!

RUTGERS

New Jersey Medical School