Cannabis, Addiction and Mental Health after Brain Injury

The ABC's of Medical Cannabis In Canada

Mark H. Kimmins, MD - June 20, 2019

COMMERCIAL DISCLOSURE

- I have Relationships with the following commercial interests:
  - President of Natural Health Services
  - Medical Director Sunniva.
  - Chair of Medical Advisory Board.
- This program has received financial support from Sunniva in the form of Educational Grants.

OBJECTIVES

- Understand history of medical cannabis use
- Understand difference between medical and recreational use
- Understand current scientific research supporting medical cannabis
- Understand potential role of medical cannabis in brain injury and neurology
- Understand the role of health care providers in harm reduction approach

ASSUMPTIONS

"All ethical standards and best medical practices to which providers adhere to when prescribing medications, remain applicable when recommending medical cannabis"

Mark H. Kimmins MD

FRCSC, FACS, FASCRS

President Natural Health Services

Medical Director, Sunniva

Chair of Medical Advisory Board

WHERE DID WE START?

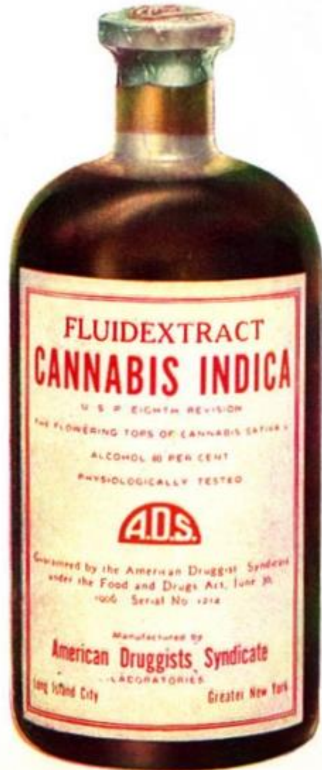
LONG HISTORY OF HUMAN USE

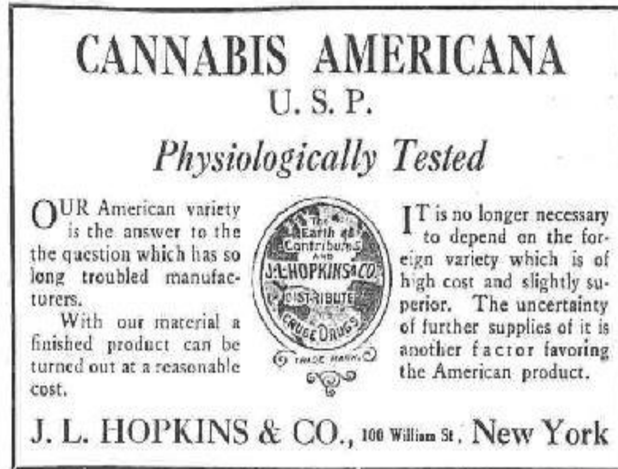
- Humans have been growing/using cannabis for more than **10,000 years**.
- Documented medical use of cannabis can be traced back at least **5,000 years** to ancient China and Egypt.
- **150 AD**, Chinese surgeon Hua T'uo used a mixture of wine and cannabis as a surgical anaesthetic.
- **In 1839**, Irish physician Dr. William B. O'Shaughnessy published on the Preparations of the Indian Hemp, or Gunjah reviewing the use of cannabis in rheumatism, rabies, cholera, tetanus, cramps and delirium tremens.

HISTORY IN NORTH AMERICA

By the late 19th Century, cannabis-based medications were manufactured by Burroughs-Wellcome & Co., Bristol-Meyers Squib, Parke-Davis, and Eli Lilly and were widely available.

HISTORY IN NORTH AMERICA





CANNABIS AMERICANA
(Cannabis sativa—American grown)
PHYSIOLOGICALLY TESTED
DOSE—1-5 to 1 grain
ELI LILLY & CO.
INDIANAPOLIS
U. S. A.

ONE-FOURTH POUND—SOLID EXTRACT
CANNABIS AMERICANA
PHYSIOLOGICALLY TESTED
(Cannabis sativa—American Grown)
Analgesic, Hypnotic, Antispasmodic and powerful Narcotic
DOSE—1-5 to 1 grain
OCT 11 1913

Image attributions: Public Domain, https://commons.wikimedia.org/w/index.php?curid=146985

THEN… PROHIBITION STARTS

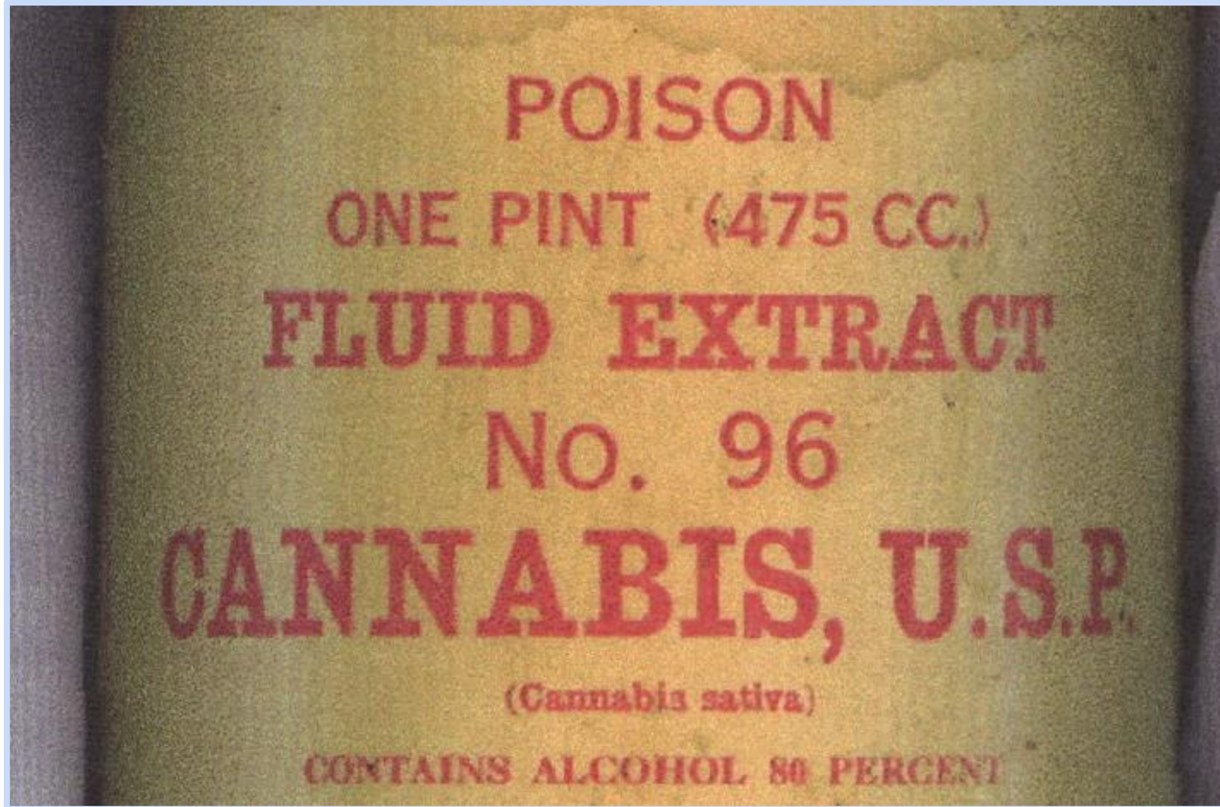


Image attributions: By Unknown - http://www.AntiqueCannabisBook.com, Public Domain, https://commons.wikimedia.org/w/index.php?curid=2398154

HOW WAS CANNABIS MEDICINE REINTRODUCED?

- Baby Boom and Gen X - personal experience and social observation
- La Guardia report, Shafer Report, Le Dain Commission
- National Organization for the Reform of Marijuana Laws (NORML)
- Discovery of the Endocannabinoid system (1992)
- Support for medical cannabis has come from citizen support via lobbying, activism and through the courts (In US through ballot)

POTENTIAL MEDICAL USES OF CANNABIS: NIH & IOM REVIEWS IN LATE 90s

The NIH Workshop on the Medical Utility of Marijuana (1997) and the Institute of Medicine (1999), following thorough review, identified medical conditions warranting further research regarding the possible therapeutic effects of cannabis:

- Appetite stimulation
- Nausea and vomiting
- Analgesia
- Neurological and movement disorders

POTENTIAL MEDICAL USES OF CANNABIS IN BRAIN INJURY: NIH Study 1998

- **Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants**

  Proc Natl Acad Sci USA. 1998 Jul 7;95(14):8268-73

  Hampson AJ, Grimaldi M, Axelrod J, Wink D

- **Neuroprotective antioxidants from marijuana.**

  Ann N Y Acad Sci. 2000;899:274-82.

  Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J.

POTENTIAL MEDICAL USES OF CANNABIS: USA Patent 6,630,507 B1

- Filed April 21st 1999
- Granted October 7, 2003

- Patent: **CANNABINOIDS AS ANTIOXIDANTS + NEUROPROTECTANTS**

- Assignee: The United States of America as represented by the Department of Health and Human Services, Washington DC

STATUS IN CANADA

- **1923** - Outlawed *(1937 in US)*
- **1972** - Le Dain Commission
- **2001** - Medical Marijuana Access Regulations (MMAR)
- **2013** - Marijuana for Medical Purposes Regulations (MMPR)
- **2016** - Access to Cannabis for Medical Purposes Regulations (ACMPR)
- **2017** - Proposed Cannabis Act
- **2018** - Cannabis Act, Oct 17, 2018

CANNABIS ACT - 2018

Government of Canada | Gouvernement du Canada

What is legal as of October 17, 2018 - Subject to provincial or territorial restrictions Adults who are 18 years of age or older are legally able to:

- Possess up to 30 grams of legal cannabis, dried or equivalent in public
- Share up to 30 grams of legal cannabis with other adults
- Buy dried or fresh cannabis + cannabis oil from a provincially-licensed retailer
- Grow, from licensed seed/seedlings, up to 4 cannabis plants per residence
- Make cannabis products, such as food and drinks, at home

Cannabis edible products and concentrates will be legal for sale approximately one year after the ***Cannabis Act*** came into force (ie: October 2019)

CANNABIS ACT - 2018

Government of Canada　Gouvernement du Canada

Patients authorized by their health care provider are still able to access cannabis specifically for medical purposes by:

- Buying directly from a federally Licensed Producer
- Registering with health Canada to produce a limited amount of cannabis
- Designating someone to produce it for them

Subject to legal age limit in province or territory, they are also able to buy:

- At provincial or territorial authorized retail outlets
- Through provincial or territorial authorized online sales platforms

CANNABIS ACT - 2018

Government of Canada   Gouvernement du Canada

- New regulations remove personal storage limits for patients.
- Any adult Canadian can store as much cannabis as they want at home.
- Public possession limits remain the same for authorized patients who are registered with a federally licensed seller or with Health Canada:
    - The lesser of 150 grams or a 30-day supply of dried cannabis (or the equivalent) in addition to the 30 grams for non-medical purposes

NOTICE OF INTENT TO AMEND: PRESCRIPTION DRUG LIST (PDL): PHYTOCANNABINOIDS

Government of Canada Gouvernement du Canada

The purpose of the Notice of Intent to Amend is to announce that Health Canada will :

Add phytocannabinoids to the Human and Veterinary Prescription Drug Lists (PDL)

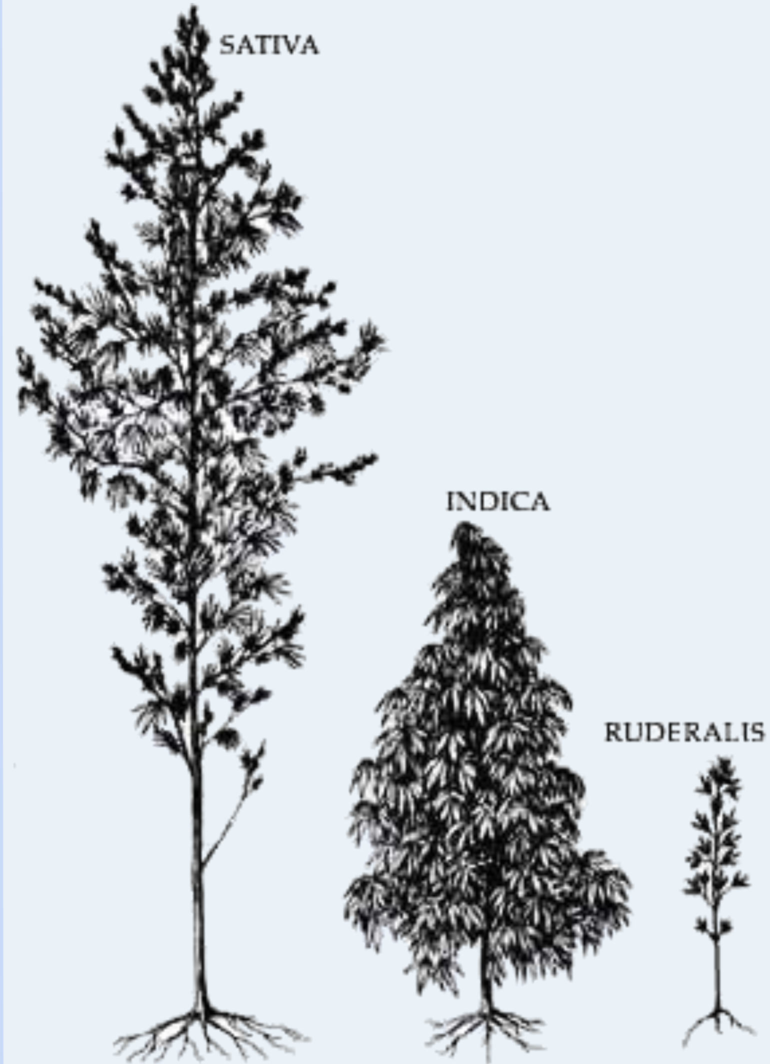
This addition will be effective upon the coming force of the Cannabis Act.

- Interpretation is that only limited recreational products will be excluded
- Enforcement and interpretation remain unclear.

CANNABIS: THE PLANT

CANNABIS: THE PLANT

- Cannabis is the proper term for the genus.
- Cannabis is dioecious, i.e. it does not self-pollinate - individual plants are male or female.
- Female plant produces flowers from which medical products are made.
- Male plants are used when pollination is required.



CANNABIS: TRICHOMES

- Trichomes are resin glands found on the flowers and leaves of the plant.
- This sticky resin contains concentrated chemicals, including cannabinoids, terpenes and flavonoids.

CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

DEFINITIONS

Cannabinoids

- Compounds that act on cannabinoid receptors in the human body

Endocannabinoids

- Cannabinoids that are naturally produced in the body (endogenous)

Phytocannabinoids

- Cannabinoids produced by the cannabis plant

Synthetic Cannabinoids

- Laboratory-synthesized compounds that bind to cannabinoid receptors, may be used as pharmaceuticals (i.e. Nabilone, Marinol)

Terpenes

- Aromatic Hydrocarbons. Essential Oils

Flavonoids

- Polyphenol plant compounds with antioxidant properties - Plant pigments

Medical Vs Recreational Cannabis

Same plant as source for both product lines

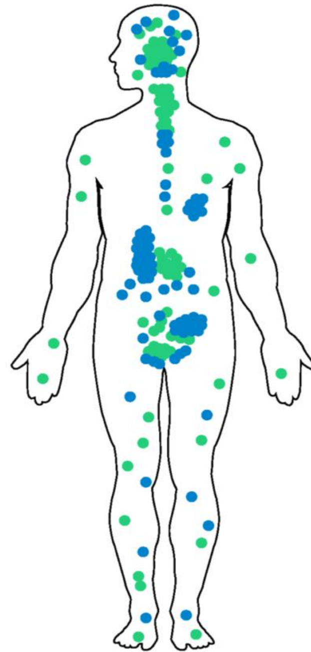
Recreational

- Intention of user is euphoria, and some degree of intoxication
- Traditionally smoked as whole plant material
- Recreational concentrates for vaporization becoming more common
- High THC Low CBD
- Macro-dosing common

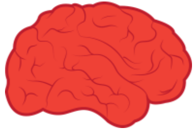
Medical

- Intention of user is relief of symptoms without impairment
- Traditionally offered as tinctures or extracts
- Oral formulations like pills, gelcaps, tablets are most popular
- High CBD Low THC
- Pharmaceutical grade extracts
- Micro-dosing common

How does Cannabis work?
How can it treat so many symptoms?

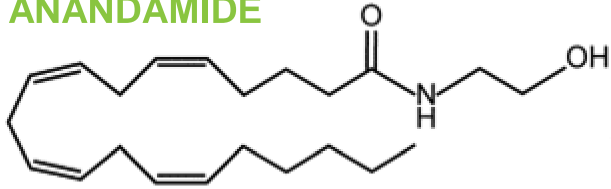


THE ENDOCANNABINOID SYSTEM

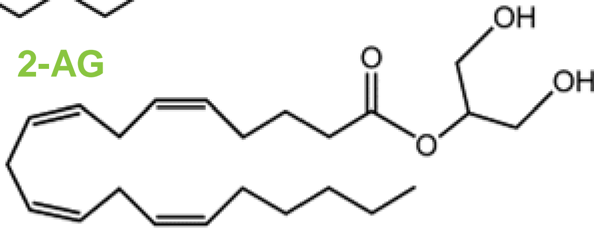


ENDOCANNABINOIDS

ANANDAMIDE

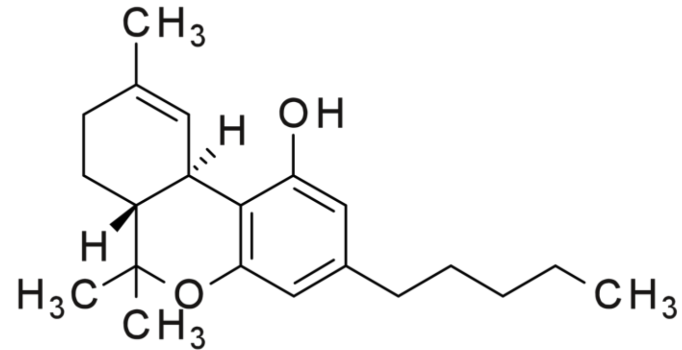


2-AG



PLANT CANNABINOID

THC

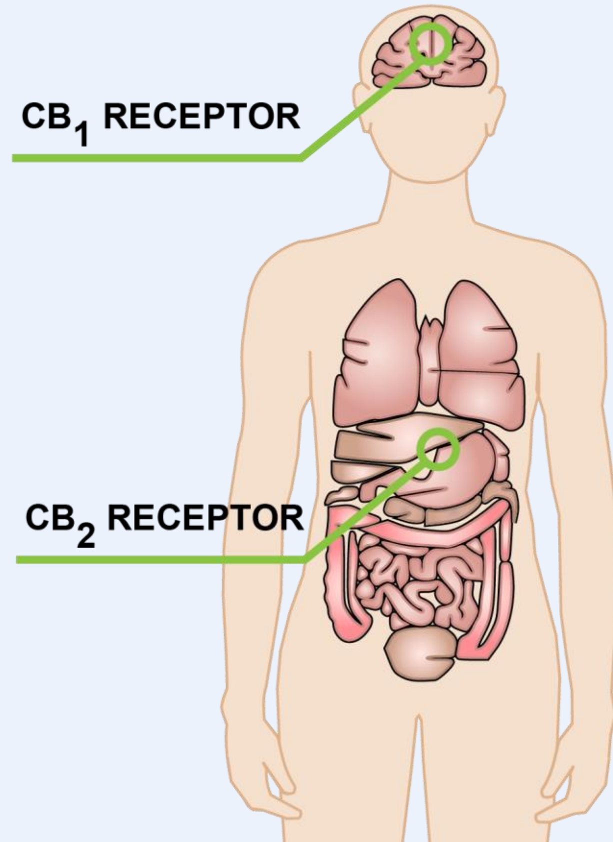


- Endocannabinoids include Anandamide and 2-Arachidonylglycerol (2-AG)
- ? N-Arachidonyl dopamine (NADA)

THE ENDOCANNABINOID SYSTEM

- Active cannabinoid compounds affect the body through specific cannabinoid receptors:
  - **CB1** - central and peripheral nervous system
  - **CB2** - Peripheral tissues + immune system

HOMEOSTASIS mechanisms related to multiple physiologic processes



THE ENDOCANNABINOID SYSTEM

- Modulator of neurotransmitter pathways
- Homeostasis mechanisms related to multiple physiologic processes

- Inflammation
- Appetite
- Metabolism
- Cardiovascular function
- Bone density
- Synaptic plasticity
- Pain
- Memory
- Sleep
- Reward/addiction
- Stress regulation
- Mood
- Reproduction
- Digestion
- Endocrine function

THE ENDOCANNABINOID SYSTEM

- **Deficiencies or alterations of the ECS may contribute to human disease**
- Abnormalities of the Endocannabinoid system likely play a crucial role in the pathophysiology of multiple human diseases.
- Multiple components of the ECS system are now seen as potential therapeutic targets for cannabis based medicines.

Curr Clin Pharm. 2016;11(2):110-7

CANNABIS PHYTO-CHEMISTRY

CANNABINOIDS

- CBG
- CBGV
- THC
- THCV
- CBD
- CBDV
- CBC
- CBCV

TERPENOIDS

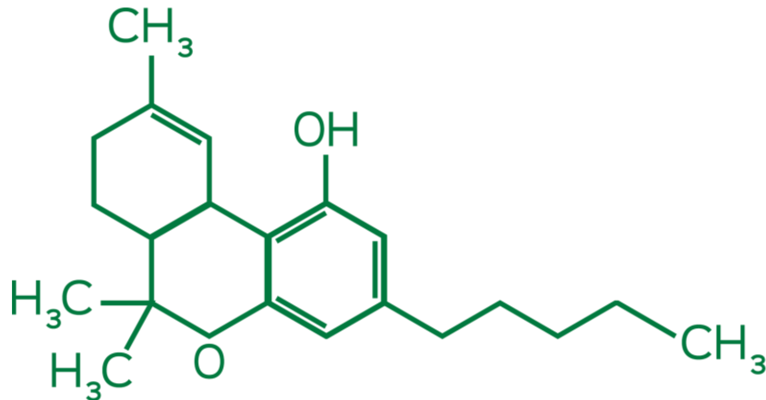
- Linalool
- Caryophyllene
- Pinene
- Humulene
- Limonene
- Myrcene

FLAVONOIDS

- Quercetin
- Apigenin
- Cannaflavin A + B
- Luteolin
- Orientin

TETRAHYDROCANNABINOL (THC)

- Δ9-THC - most well known and well studied cannabinoid
- Responsible for most of the psychotropic effects of cannabis.

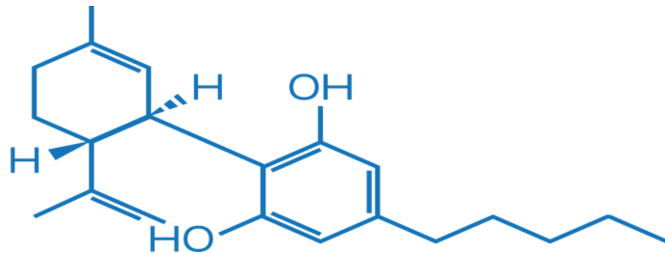


THC has multiple proven therapeutic effects:

- Pain relief
- Nausea and vomiting
- Appetite stimulant
- Insomnia
- Glaucoma
- PSTD

CANNABIDIOL (CBD)

- Major plant cannabinoid with little to no psychoactive properties
- Complex and poorly understood mechanisms of action
- CBD activates 5-HT1A serotonin receptor
- Can counteract negative effects of THC



Known therapeutic effects include:

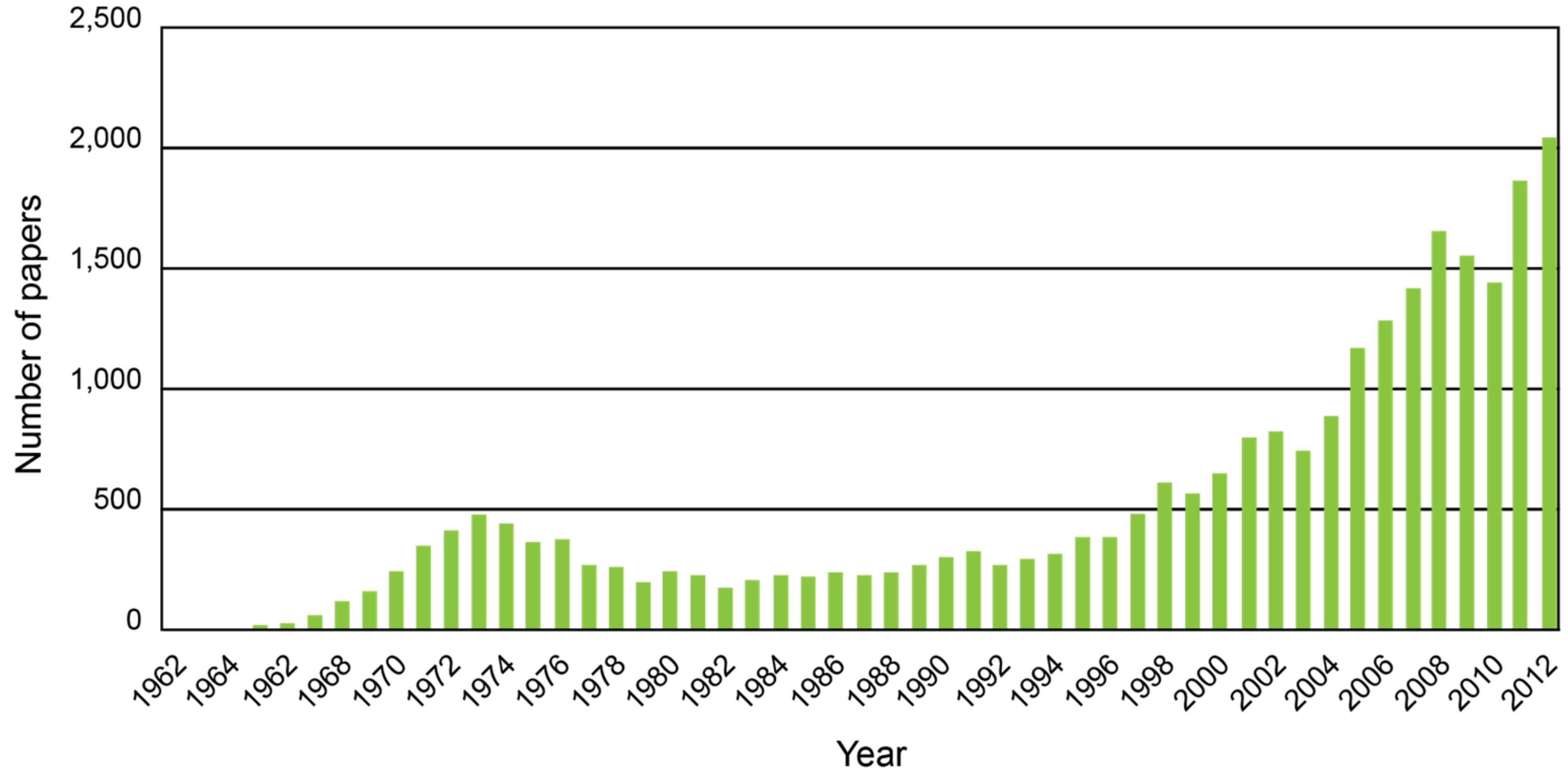
- Anti-epileptic
- Anti-anxiety
- Analgesic
- Anti-inflammatory
- Opioid and alcohol withdrawal
- Potentially anti-carcinogenic

PHYTO-CANNABINOID RATIO

Delta-9-tetrahydrocannabinol THC (Δ9-THC)	Cannabidiol (CBD)
Δ9-THC is a partial agonist at CB1 and CB2 receptors	Does not bind to either CB1 or CB2 receptors
Responsible for psychoactive effects	Affects the activity of ion channels, receptors, and enzymes
Analgesic Anti-emetic Anti-spasmotic Appetite-stimulating	Anti-inflammatory Analgesic Anti-nausea Anti-emetic Anti-psychotic Anti-ischemic Anxiolytic Anti-epileptiform

CLINICAL EVIDENCE

GROWING BODY OF RESEARCH



CLINICAL EVIDENCE

Levels of Evidence for Therapeutic Studies

LEVEL	TYPE OF EVIDENCE
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual cohort study (including low quality RCT, eg <80% follow-up)
2C”	“Outcomes” research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual case control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or “first principles”

Source: The Centre for Ebvidence Based Medicine http://www.cehm.net

LACK OF RIGOROUS LARGE TRIALS

- Approx 20,000 indexed Cannabis publications on Pub-Med
- Majority of publications are basic science, pre-clinical, or observational.

Level 1a evidence lacking

- **Systematic reviews (with homogeneity) of randomized controlled trials**

Level 1b evidence is lacking

- **Individual randomized controlled trials (with narrow confidence interval)**

CONSEQUENTLY RESULTS OF METANALYSIS WILL BE EQUIVOCAL

LACK OF RIGOROUS LARGE TRIALS

SIMPLIFIED GUIDELINE FOR PRESCRIBING MEDICAL CANNABINOIDS IN PRIMARY CARE

Canadian Family Physician - February 2018

Conclusion:

- We recommend against use of medical cannabinoids for most medical conditions owing to lack of evidence of benefit and known harms - Strong Recommendation.
- Potential exceptions are some types of pain, CINV, and spasticity due to MS or SCI.

LACK OF RIGOROUS LARGE TRIALS

CANNABIS-BASED MEDICINES FOR CHRONIC NEUROPATHIC PAIN IN ADULTS

Cochrane Systematic Review - March 2018

Conclusion:

- Cannabis-based medicines probably increase the number of people achieving pain relief of 30% or greater compared with placebo
- The potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms.
- The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes.

LACK OF RIGOROUS LARGE TRIALS

CANNABIS AND CANNABINOIDS FOR THE TREATMENT OF PEOPLE WITH CHRONIC NONCANCER PAIN CONDITIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CONTROLLED AND OBSERVATIONAL STUDIES

PAIN – October 2018

Conclusion:

- It seems unlikely that cannabinoids are highly effective medicines for CNCP
- Long-term efficacy and safety are unknown

WHAT EVIDENCE DO WE HAVE?

2013 Int J Drug Policy:

- Canadians who used cannabis for medical purposes mostly used it to treat:
    - Pain
    - Anxiety
    - Sleep disturbance

Same results as 2018 clinic survey

HEALTH CANADA 2013

Health Canada Santé Canada

- The Endocannabinoid System
- Clinical Pharmacology
- Dosing
- Therapeutic Uses
- Adverse Effects
- Warnings/Precautions
- Overdose/Toxicity

Health Canada. Information for Health care Professionals, Cannabis (marihuana, marijuana) the cannabinoids.

NATIONAL ACADEMIES REPORT (2017)

Evidence for Therapeutic Benefits of Cannabis

- Substantial/conclusive evidence of cannabinoid efficacy in:
  - Chronic pain
  - Spasticity of multiple sclerosis
  - Control of nausea
- Moderate evidence of cannabinoid efficacy in:
  - Improving sleep in those with chronic medical conditions, e.g., chronic pain, fibromyalgia, etc.
- Limited evidence of cannabinoid efficacy in:
  - Treatment of certain anxiety disorders and PTSD
  - Promoting appetite and weight gain
- No or insufficient evidence of cannabinoid efficacy in:
  - Treatment of cancers, irritable bowel syndrome, epilepsy, movement disorders due to Huntington Disease or Parkinson Disease, Schizophrenia

The Health Effects of Cannabis and Cannabinoids. Washington (DC): National Academies press (US); January 2017

TRIAL OF CANNABIDIOL FOR DRUG-RESISTANT SEIZURES IN THE DRAVET SYNDROME

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

N Engl J Med 2017; 376:2011-2020

Randomized double blind, placebo-controlled trial of 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary endpoint was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period.

LOW-DOSE VAPORIZED CANNABIS SIGNIFICANTLY IMPROVES NEUROPATHIC PAIN

Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H
J Pain. 2013 Feb;14(2):136-48

ABSTRACT

Double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Thirty-nine patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling medium-dose (3.53%), low-dose (1.29%), or placebo cannabis with the primary outcome being visual analog scale pain intensity. Psychoactive side effects and neuropsychological performance were also evaluated. Mixed-effects regression models demonstrated an analgesic response to vaporized cannabis. There was no significant difference between the 2 active dose groups' results ($P > .7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium- versus low-dose. As these NNTs are comparable to those of traditional neuropathic pain medications, cannabis has analgesic efficacy with the low dose being as effective a pain reliever as the medium dose. Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours. Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain.

The analgesia obtained from a low dose of delta-9-tetrahydrocannabinol (1.29%) in patients, most of whom were experiencing neuropathic pain despite conventional treatments, is a clinically significant outcome. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning...

2013 Feb;14(2):136-48. doi: 10.1016/j.jpain.2012.10.009. Epub 2012 Dec 11.

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, and Jean-Paul Collet, MD PhD

METHOD: 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. Further long-term safety and efficacy studies are indicated

CMAJ 2010. DOI:10.1503/cmaj.091414

CHRONIC PAIN

BJCP British Journal of Clinical Pharmacology

- Systematic review of RCTs examining cannabinoids in the treatment of chronic non-cancer pain, including neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.
- Overall the quality of trials was excellent. A majority of the trials – 15/18 – reported significant analgesic effects of cannabinoid therapy vs. placebo. Several trials also reported significant improvements in sleep.

CONCLUSION:

There is evidence that cannabinoids are safe and effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.

Br J Clin Pharmacol 2011

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

- Cannabinoid therapy is significantly more effective than placebo.
- Some trials show only marginal improvements over standard anti-emetics, but patients seem to prefer cannabinoids over conventional therapy.
- In a review of US clinical trials, Musty and Rossie found that patients who had failed on standard anti-emetics experienced 70-100% relief of CINV when they smoked cannabis, while those treated with Δ9-THC capsules experienced 76-88% relief.

J Cannabis Ther 2001(1):026-56

MULTIPLE SCLEROSIS

- Multiple randomized trials. Lancet 2003
- Significant subjective improvement
- Equivocal objective improvement
- Relief of multiples symptoms (pain, spasticity, insomnia)
- American Academy of Neurology:
    - Oral cannabis and THC extracts are probably effective for reducing patient-reported symptoms of spasticity and pain
    - Sativex oral spray (GW Pharmaceuticals) is probably effective for improving patient-reported symptoms of spasticity, pain and urinary frequency

PALLIATIVE CARE

Cannabinoids can be useful in alleviating a variety of palliative symptoms:

- Intractable nausea and vomiting associated with chemotherapy or radiotherapy
- Anorexia/cachexia
- Severe intractable pain
- Depressed mood/anxiety
- Insomnia
- Decrease dosage of other medications (e.g. opioids).
- Controlled trials, with synthetic cannabinoids and dried cannabis, reported increases in Quality of Life measures.

Ann Palliat Med 2018

OPIOID EPIDEMIC

- Leading cause of accidental death in North America is drug overdose
- 72,000 lethal drug overdoses 2015
- 2/3 deaths due to opioids
- 1/3 deaths due to prescriptions
- Overdose death rate has more than quadrupled since 1999

OPIOID EPIDEMIC

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS;
Colleen L. Barry, PhD, MPP

JAMA Intern Med. 2014;174(10):1668-1673.

States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws.

Association with a lower rate of overdose mortality generally strengthened over time

Conclusion: medical cannabis laws are associated with reductions in opioid analgesic overdose mortality

OPIOID EPIDEMIC

MEDICAL MARIJUANA LAWS ASSOCIATED WITH A DECLINE IN THE NUMBER OF PRESCRIPTIONS FOR MEDICAID ENROLLEES.

Bradford AC1, Bradford WD2.

2017 May 1;36(5):945-951. doi: 10.1377/hlthaff.2016.1135. Epub 2017 Apr 19

ASSOCIATION OF MEDICAL AND ADULT-USE MARIJUANA LAWS WITH OPIOID PRESCRIBING OF MEDICAID ENROLLEES.

Hefei, Wen and Hockenberry, JM

JAMA Intern Med April 2018

ASSOCIATION BETWEEN US STATE MEDICAL CANNABIS LAWS AND OPIOID PRESCRIBING IN THE MEDICARE PART D POPULATION.

Bradfor AC, Bradford WD, Abraham A

JAMA Intern Med April 2018

Conclusion: All three studies show Medical Cannabis laws are associated with significant reductions in opioid prescribing

OPIOID EPIDEMIC

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

Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C, Oprescu AM, Salsitz E

Am J Psychiatry Published Online: 21 May 2019 https://doi.org/10.1176/appi.ajp.2019.18101191

- CBD administration, in contrast to placebo, significantly reduced both craving and anxiety
- There were no significant effects on cognition, and there were no serious adverse effects
- CBD's potential to reduce cue-induced craving and anxiety provides a strong basis for further investigation of this phytocannabinoid as a treatment option for opioid use disorder

Brain Injury and Neurology

- No major prospective human trials except for MS and epilepsy
- Evidence overall considered to be preliminary and pre-clinical but is increasing.
- Majority of studies are in vitro or in animal models.
- Wide adoption and acceptance amongst certain populations – NFL
- Benefit reported but unproven in TBI, stroke, Alzheimers, and Parkinson's
- Increased attention on CBD as both treatment and prophylaxis

Brain Injury and Neurology

Increased severity of stroke in CB1 cannabinoid receptor knock-out mice

J Neurosci. 2002 Nov 15;22(22):9771-5

- Mortality and neurologic deficits after cerebral ischemia increased in Cannabinoid receptor deficient mice.
- These findings indicate that endocannabinoid system pathways protect mice from ischemic stroke by a mechanism that involves CB1 receptors.

Brain Injury and Neurology

Endocannabinoids and traumatic brain injury

Br J Pharmacol. 2011 Aug; 163(7): 1402–1410

- The endocannabinoid system has the ability to affect the functional outcome after TBI by a variety of mechanisms.
- There is evidence of neuroprotective effects exerted by the endocannabinoid system within hours of neurologic injury.
- Protective mechanisms include inhibition of excitatory neural transmission, inhibition of the inflammatory response and reduction of vasospasm.

Brain Injury and Neurology

Early survival of comatose patients after severe traumatic brain injury with the dual cannabinoid CB1/CB2 receptor agonist KN38-7271: a randomized, double-blind, placebo-controlled phase II trial.

J Neurol Surg A Cent Eur Neurosurg. 2012 Aug;73(4):204-16

- Survival rates within 1 month of the injury were significantly better in the treatment groups than in the placebo group with no severe or serious adverse effects.

- **Conclusion:**
  CB1/CB2 agonists appeared beneficial in the acute early phase of the comatose patient after a head injury. Its use was safe and well tolerated by patients. These results may provide the basis for further phase II/III trials in larger study populations.

Brain Injury and Neurology

Effect of marijuana use on outcomes in traumatic brain injury.

Am Surg. 2014 Oct;80(10):979-83

- A THC(+) screen was independently associated with survival after TBI
- A THC (+) screen is associated with decreased mortality in adult patients sustaining TBI.
- **Conclusion:** THC + screen is a marker for cannabis use. This study suggests that cannabis may have properties associated with improved survival after TBI

Brain Injury and Neurology

Cannabidiol protects an *in vitro* model of the blood–brain barrier from oxygen-glucose deprivation via PPARγ and 5-HT_{1A} receptors

Br J Pharmacol. 2016 Mar; 173(5): 815–825

- *In vivo* and *in vitro* studies have demonstrated a protective effect of cannabidiol (CBD) in reducing infarct size in stroke models and against epithelial barrier damage in numerous disease models.
- CBD prevented the increase in permeability caused by OGD ischemia. CBD was most effective when administered before OGD, but protective effects were observed up to 2 h into reperfusion.
- Data suggest that preventing permeability changes at the BBB could represent an as yet unrecognized mechanism of CBD-induced neuroprotection in ischemic neurologic events via activation of PPARγ and 5-HT_{1A} receptors.

Brain Injury and Neurology

Modulation of Astrocyte Activity by Cannabidiol, a Non-psychoactive Cannabinoid

Int J Mol Sci. 2017 Jul 31;18(8)

- The cannabinoid system and its ligands have been shown to interact and affect activities of astrocytes which appear to play a significant role in brain physiology and pathology.
- CBD has been shown to decrease proinflammatory functions and signaling in astrocytes.
- Increased astrocyte activity is suppressed in the presence of CBD in models of ischemia, Alzheimer-like and Multiple-Sclerosis-like neurodegenerations, sciatic nerve injury, epilepsy, and schizophrenia.

Brain Injury and Neurology

Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia

Prog Neuropsychopharmacol Biol Psychiatry. 2017 Apr 3;75:94-105

- CBD 10mg/kg prevented cognitive and emotional impairments, neurodegeneration and white matter injury, and reduced glial response that were induced by brain ischemia.
- CBD also stimulated neurogenesis and promoted dendritic restructuring
- Collectively, the results demonstrate that short-term CBD treatment results in global functional recovery in ischemic mice and impacts multiple and distinct targets involved in the pathophysiology of brain injury.

Brain Injury and Neurology

Role of CB_2 Receptor in the Recovery of Mice after Traumatic Brain Injury

J Neurotrauma. 2019 Jun;36(11):1836-1846

- In a mouse model of closed head injury CB2 agonists enhanced neurobehavioral recovery, inhibition of tumor necrosis factor, increased synaptogenesis, and recovery of the cortical spinal tract.

Oral Cannabidiol Prevents Allodynia and Neurological Dysfunctions in a Mouse Model of Mild Traumatic Brain Injury

Front Pharmacol. 2019 Apr 16;10:352

- 10% oral CBD oil treatment restored behavioral alterations associated with TBI, and partially normalized cortical biochemical changes. CBD is a potential pharmacological tool to improve neurological dysfunctions caused by the traumatic brain injury.

OTHER CONDITIONS

Health Canada Santé Canada

- Amyotrophic lateral sclerosis
- Fibromyalgia
- Crohn’s
- Glaucoma
- Headache and migraine
- Motor disorders, i.e. Huntington’s, Parkinson’s
- Osteoarthritis
- Psychiatric disorders
- Rheumatoid arthritis
- Spinal cord injury
- Concussion
- Wasting syndrome
- Any debilitating condition

RISKS/ADVERSE EFFECTS

- Remarkably safe compared to other medications
- No cannabis overdose death
- Incredibly wide therapeutic index
- LD50 could not be determined

SIDE EFFECTS

- Most common acute side effects include: tacchycardia, sedation, dizziness, somnolence, dry mouth, blurred vision, postural hypotension.
- 2008 CMAJ review found 97% of 47,779 adverse effects were not serious.

ACUTE	CHRONIC
Hyperemesis syndrome	Mood disorders
Impaired coordination	Exacerbation of psychotic disorders (in vulnerable patients)
Impaired performance	Cannabis use disorder
Anxiety	Withdrawal syndrome
Suicidal ideations/tendencies	Neurocognitive impairment
Psychotic symptoms	Cardiovascular and respiratory diseases
Increased risk of motor vehicle accidents	Other diseases

Karila L, et al. Acute and long-term effects of cannabis use: a review. Curr Pharm Des 2014;20(25):4112-8.

DRUG INTERACTIONS

- No reported severe drug interactions or absolute contra-indications
- Very little good data, particularly with specific medical cannabis preparations
- Primary recommendation is to avoid use of any CNS depressants or major sedatives with cannabis, as effects can be compounded
- Theoretical risk associated with cytochrome-P450 metabolism
- Variable effects reported with anti-coagulants
- Possible reduction of effects of theophylline and epileptic drugs

CONTRA-INDICATIONS

- No absolute contraindications
- Patients underage 18/25
- Patients with severe cardiac disease
- Patients with severe respiratory disease
- Patients with severe hepatic or renal dysfunction
- Patients with personal or family history schizophrenia
- Patients with current or past history of substance abuse
- Patients on current psychoactive medications
- Patients who are pregnant or breastfeeding
- Patients with history of severe adverse effect or allergy

DOSAGE & ADMINISTRATION

DOSAGE FORMS

Medical cannabis can be provided for ingestion or vaporization

Dried cannabis and cannabis oils are available from LPs

Smoking is not recommended

What is Average Daily Dose?

- A Danish study of 5,000+ patients reported average daily dose of dried cannabis of 0.68 grams/day (range of 0.65 to 0.82 grams/day)
- In Israel, data from their medical marijuana program revealed an average daily amount of ~1.5 grams of dried cannabis/day.
- Health Canada Data – 1st quarter 2018 = 2.1 g/day average authorization

DOSING & TITRATION

- Remarkable reported dosing range in active patients 1mg – 2000mg
- Extremely wide therapeutic index
- NEJM study 20mg/kg CBD dose associated with minimal side effects
- Known paradoxical response at higher doses. Opposite to intended effects.
  The Journal of Pain. 2012;13(5):438-449.
- Most patients do best at lowest dose titrated to relief of symptoms

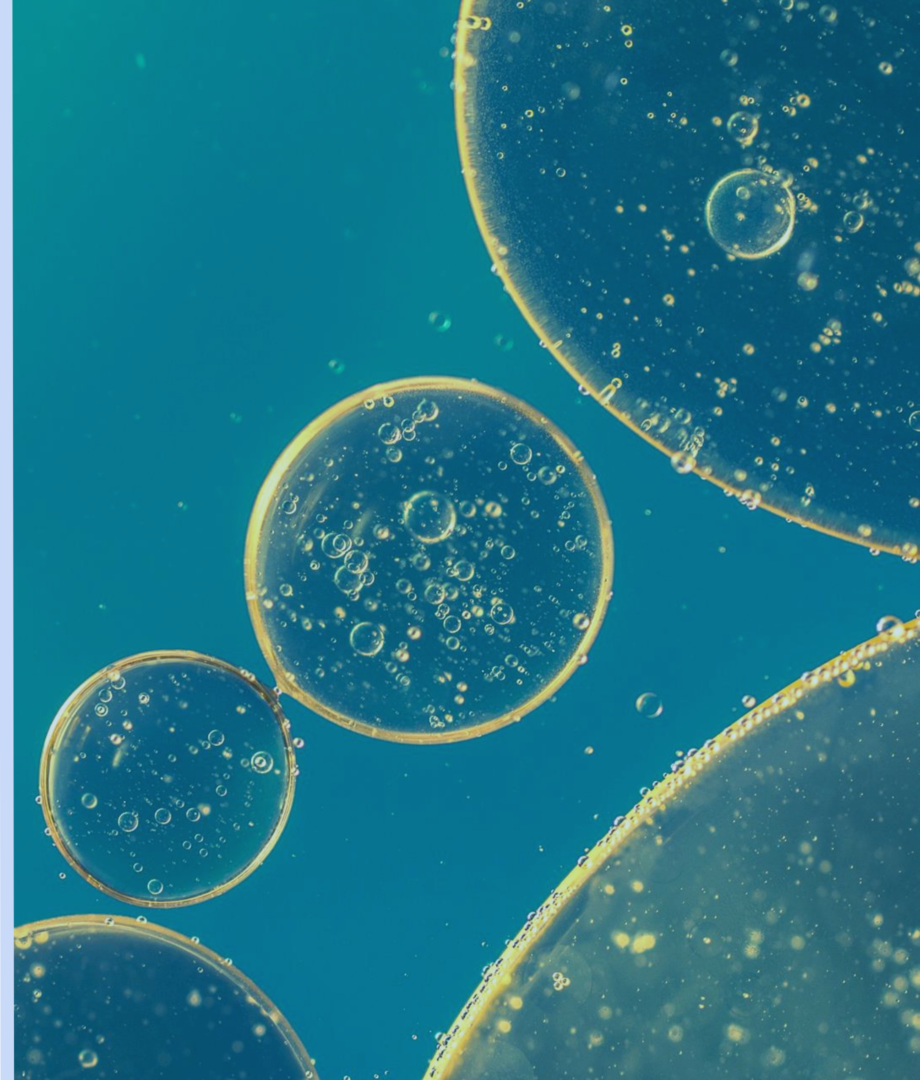
DOSING

START LOW AND GO SLOW

- Keep dose as low as possible to control symptoms.
- Start with 1 ‘puff’ of inhaled cannabis, or 1-2 drops tincture or oil. Start q daily or BID
- Define a clear clinical endpoint, and adjust dosage to achieve that goal.
- Dose titration requires active patient participation
- Detailed daily diary is a good tool to evaluate therapy.

DOSING & TITRATION

- Industry standard edible dose = 10mg
- Start with ¼ to ½ standard dose
  - 2.5 - 5 mg q.d. - q.i.d. (THC and CBD)
- Oil droppers have graduated measurement markers.
- Dosage equivalency on labels
- Typically 2 drops = 0.1ml = 2.5mg



DOSING & TITRATION

- **Vaporization:**
  - Flower buds vary in potency
    - 10 - 20% THC
    - 0.5g = 50 - 100 mg THC
    - 20 puffs = 2.5 - 5mg
    - Start 1 mid inhalation puff

CANNABIS USE FOR INPATIENTS

Challenges

- Cannabis medicine is federally legal and approved by Health Canada
- Cannabis medicines are not on formulary
- Patients are able to access wide range of cannabis products
- Authorized Medical Document does not allow HCP to dictate product purchase
- Both recreational and medical products are available
- No set dosing or frequency guidelines

CANNABIS USE FOR INPATIENTS

Approach

- HCP must decide whether continuation of therapy is appropriate
- Emphasis on patient safety, comfort and well being
- Established policies, procedures, and bylaws should guide approach
- Use non-formulary drug policy and alcohol policy as guides
- Follow established no-smoking guidelines and policies

CANNABIS WITHDRAWAL SYNDROME

- Evidence from animal and human studies indicate that cessation from long-term and regular cannabis use may precipitate a specific withdrawal syndrome
- Cannabis withdrawal syndrome is typically mild and non-life threatening, but can delay discharge and recovery
- Risk higher in patients with poor coping ability or mental health conditions
- Risk higher with ploy-drug use

Subst Abuse Rehabil. 2017; 8: 9–37

CANNABIS WITHDRAWAL SYNDROME

Symptoms include:

- Anxiety and feeling of dissociation
- Restlessness
- Irritability
- Poor appetite
- Disturbed sleep
- Vivid dreams
- Night sweats
- GI Upset
- Resting tremor

Symptoms usually peak in 2-5 days but may last longer

(Sativex) Nabiximols 1:1 THC:CBD

- Oral mucosal spray
- Extract of Cannabis sativa
- Each spray contains 2.5mg THC and 2.5mg CBD
- Cannabinoids appear to be the most effective treatment for cannabis withdrawal syndrome
- Nabiximols significantly reduces overall severity of cannabis withdrawal

CNS Drugs. 2018 Oct 25 pp 1-17 *JAMA Psychiatry. 2014;71(3):281-291*

Role of Health Provider

- Medical Document requires licensed Health Care Provider authorization
- Cannabis medicine remains a highly individualized therapy that requires active physician and provider engagement.
- Dose and frequency of use are determined through active titration and journaling
- Goal of therapy is relief of symptoms without impairment.
- Patient function and well being is paramount

Role of Health Provider

- Harm reduction approach is key
- Use cannabis medicine to treat multiple symptoms and reduce polypharmacy
- Use cannabis medicine to reduce dependency on opiates and benzodiazepines
- Help patients access clean, regulated, safe medically specific cannabis products from Licensed Producers

Role of Health Provider

- Become familiar with the evidence supporting cannabis medicine
- Become comfortable with “Start low and Go Slow” approach.
- Develop relationships with cannabis medicine experts and legitimate clinics
- Keep an open mind and realize that there are still many unanswered questions
- EBM means making decisions with “best available evidence”.
  It doesn’t mean certainty

CONCLUSION

SUMMARY

- Long history of medical cannabis use.
- Recent prohibition not based on science.
- Multiple therapeutically active compounds in cannabis.
- Research shows benefit in multiple disease states but we lack phased drug trials, and large methodologically rigorous RCT's.
- Relief of multiple symptoms, improve QoL, and reduction of opioids and other medications.
- Unparalleled safety record

SUMMARY

- Guidelines for use in brain injury and neurology are still being developed
- Therapy requires active patient and provider engagement
- Medical cannabis is just medicine and existing policy can be applied
- Licensed Producers are extensively regulated
- Providers should educate themselves and be informed and comfortable
- Recreational legalization has increased the demand for medical cannabis
- Still many unanswered questions

QUESTIONS?