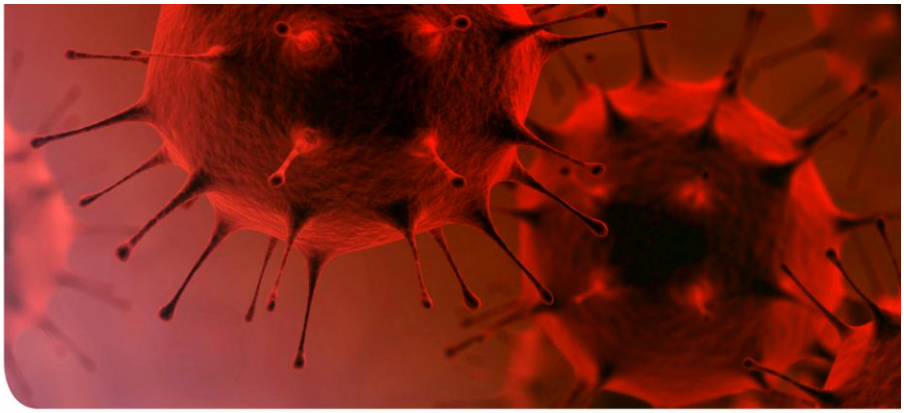


An Introduction to Medical Cannabis

May 12th, 2018

Dr. Danial Schecter, MD, CCFP
Co-Founder, Cannabinoid Medical Clinic
Chief Medical Advisor, Auscann

Learning objectives

By the end of this presentation the learner will be able to:

- Understand the scientific rationale for prescribing cannabinoids
- Review how cannabinoids can affect various symptoms including pain, nausea/vomiting, insomnia and anxiety
- Review safety, toxicity and adverse events associated with medical cannabis

Why Cannabinoid Medicine

- Awareness of the endocannabinoid system
- Available pharmaceutical agents for certain indications often have limited efficacy or intolerable side effects
- Many patients report improvement in symptoms and quality of life

Cannabinoids… A Class of their Own

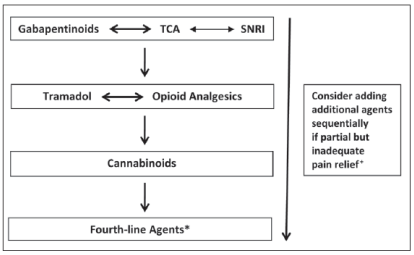
CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

"The cannabinoids are analgesic agents with increasing evidence of efficacy in central NeP states, with a combined NNT of 3.4"

- 2014



Cannabinoids… A Class of their Own

European Journal of Neurology 2010, **17:** 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

- HIV associated painful polyneuropathy: Only lamotrigine, smoking cannabis, capsaicin patches were found moderately useful
- Central neuropathic pain: Cannabinoids in MS associated pain only if all other treatments fail
- Cannabinoids (level A in MS and peripheral NP) are proposed for refractory cases

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Medical Cannabis Is Not a Novel Concept…

2800 BCE – present in pharmacopoeia of Chinese Emperor Shen Nung

70 CE – Roman physician Dioscorides records medical properties

1788 – plants sent to Australia by Sir Joseph Banks on the First Fleet

1870 – listed in US Pharmacopoeia

1890 – prescribed by Queen Victoria's personal physician

Eli Lilly, Parke-Davis (now owned by Pfizer) and Squibb of Bristol-Myers Squibb all sold medical marijuana at the turn of the century

Almost 6% of all manufactured drugs at the turn of the century contained cannabis in one form or another

1930s – prohibition

1996 – compassionate medical use in California

2001 – medical use federally approved in Canada

2018 – medical use federally approved in Australia, Germany, Colombia, Italy, Czech Republic, many US states and others…

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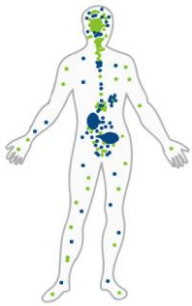
Some Definitions

- **Cannabinoids** are a class of compounds that interact with the endocannabinoid system in the human body
- **Endocannabinoids** are cannabinoids that are naturally produced in the body (endogenous)
- **Phytocannabinoids** are cannabinoids produced by the cannabis plant
- **Synthetic cannabinoids** are laboratory-synthesized compounds that bind to cannabinoid receptors

The Endocannabinoid System

- Lipid signalling system
- Found in virtually every tissue, organ and system
- Important homeostatic function in physiologic and pathophysiologic processes including (but not limited to):
  - Pain
  - Appetite/digestion
  - Sleep/wake
  - Psychiatric disease



Health Canada's document *Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids.* Available at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php

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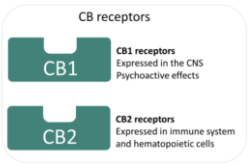
The Endocannabinoid System

Components of the endocannabinoid system:

- Endogenous Cannabinoids:
  - Anandamide or AEA (“Ananda” = Sanskrit for “bliss”)
  - 2-arachidonyl-glycerol or 2-AG
- Cannabinoid Receptors:
  - CB-1 – Found in the CNS/PNS/GI Systems
  - CB-2 – Found in the Immune System
- Enzymes:
  - FAAH and MAGL (degrading)
  - NAPE and DAGLE (synthesizing)



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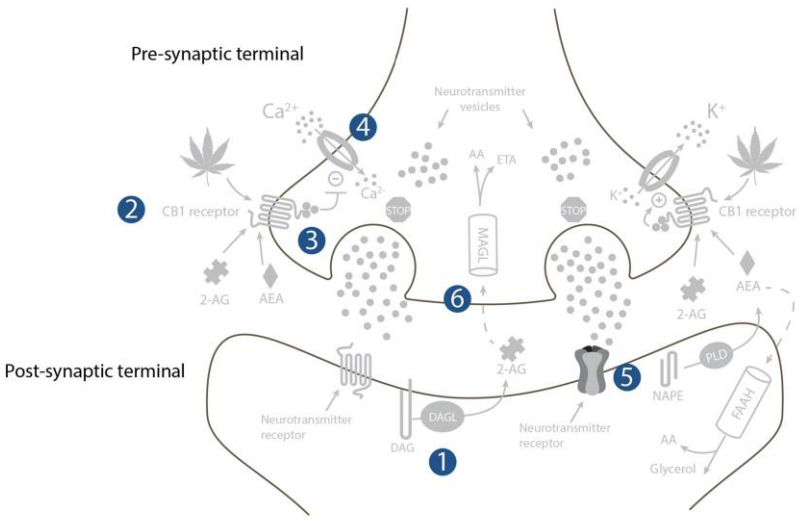

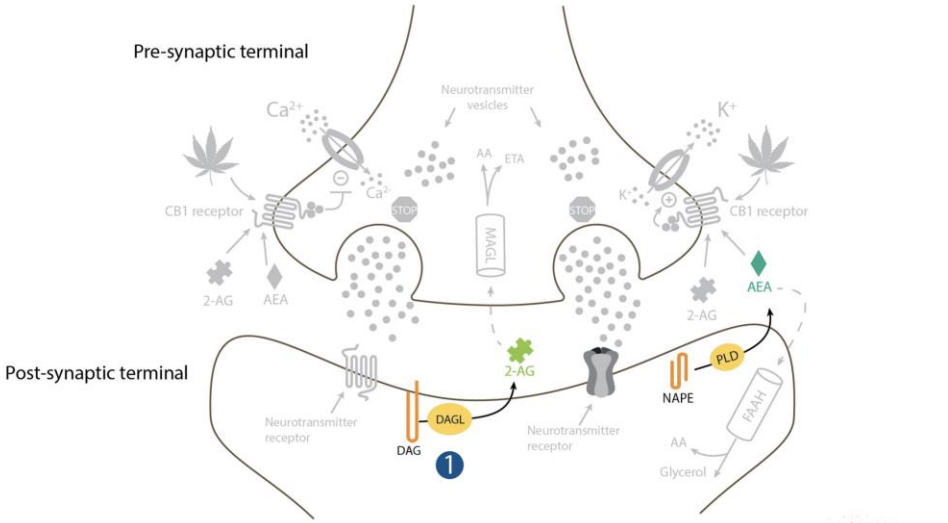
Pre-synaptic terminal
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K^+
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CB1 receptor
CB1 receptor
STOP
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MAGL
2-AG
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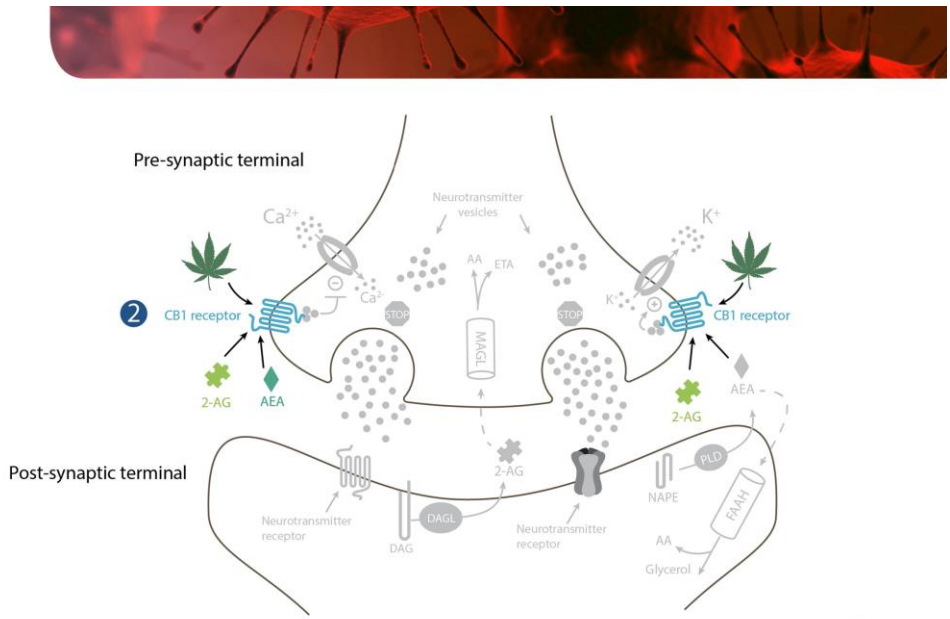
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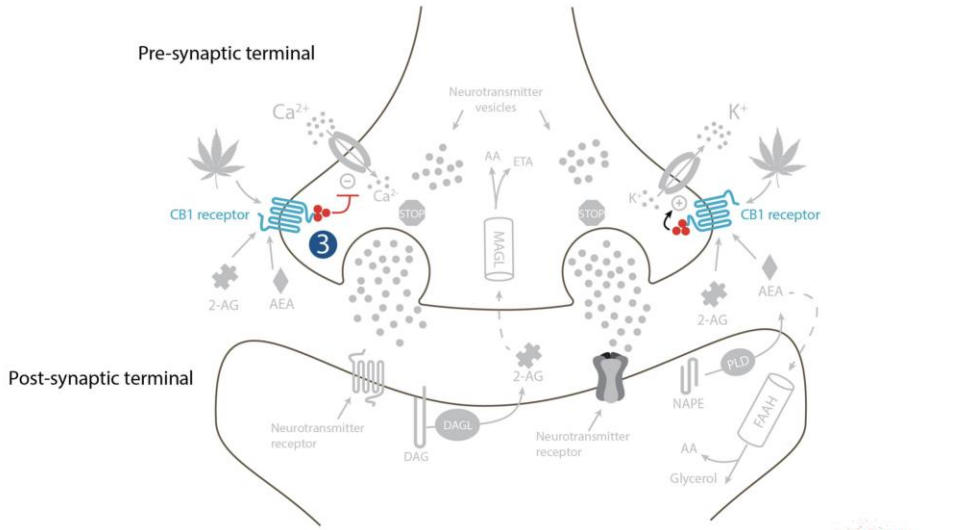
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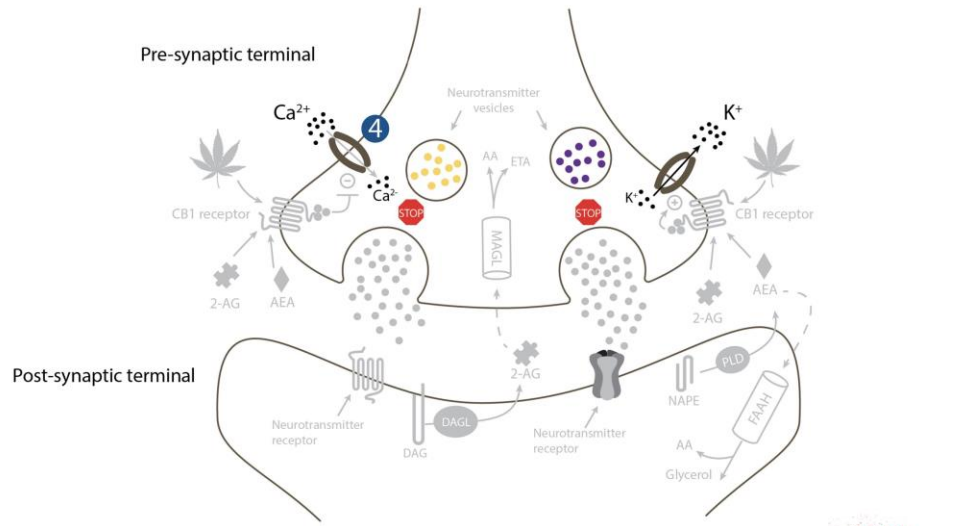
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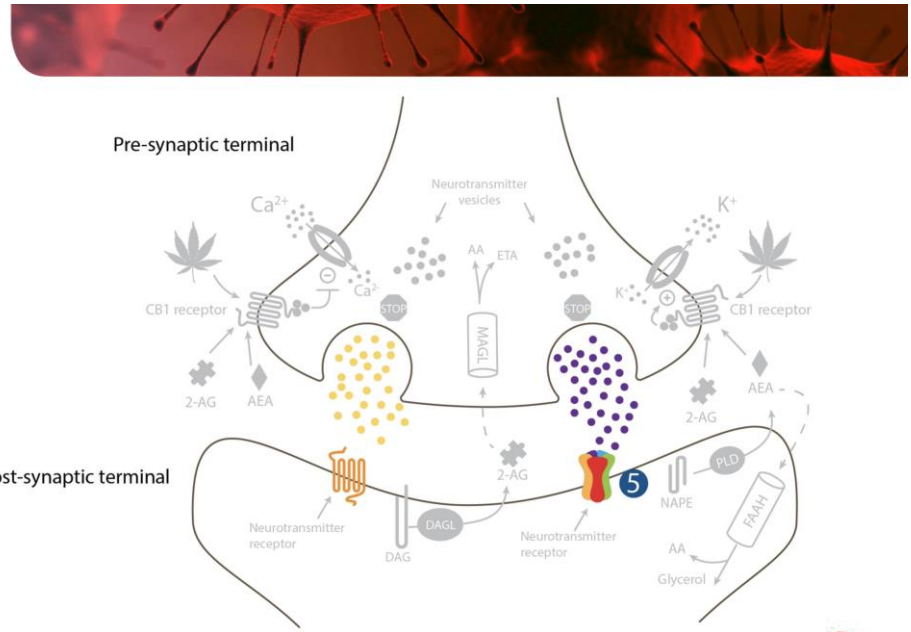
Glycerol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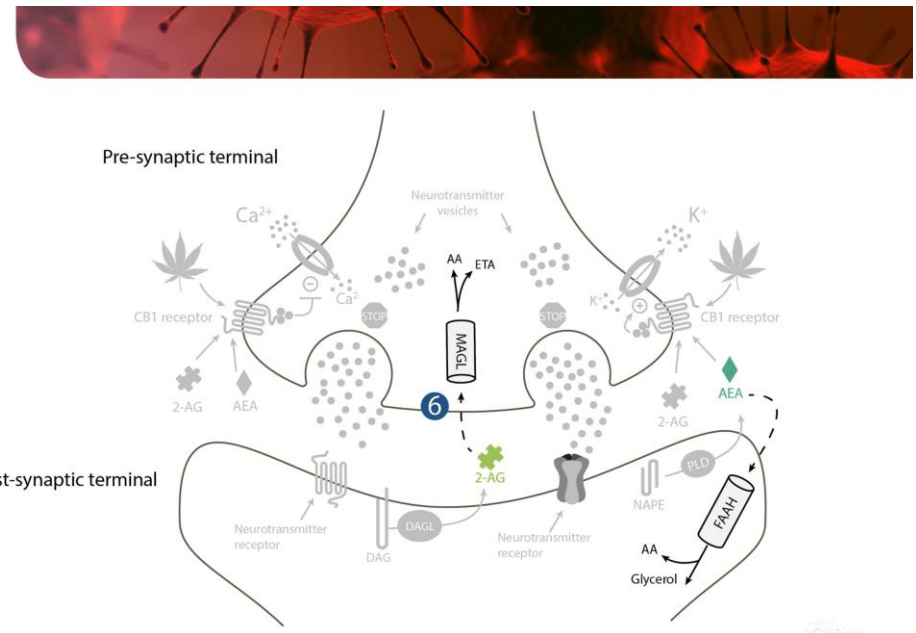
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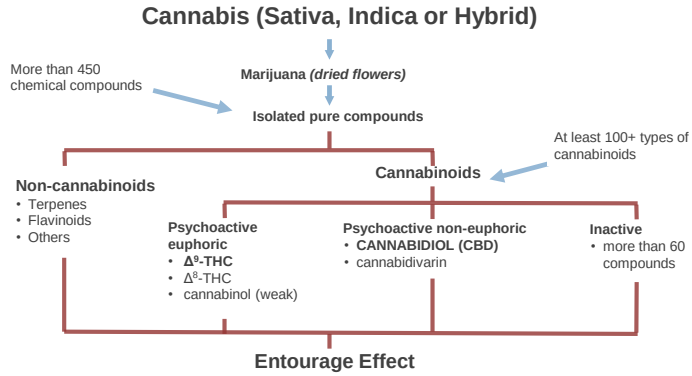
Glycerol

What is in Marijuana/Weed/Pot?



Kalant 2001. Russo, E. B. (2011), Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology*, 163: 1344–1364. doi: 10.1111/j.1476-5381.2011.01238.x

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THC versus CBD

THC (Tetrahydrocannabinol)	CBD (Cannabidiol)
Partial agonist of CB1 and CB2 receptors	Antagonist with low affinity for CB1 and CB2 receptors – affects activity of other enzymes and receptors
Euphoric inducing (feeling "high")	Non-euphoric; opposes action of THC (makes the "high" more tolerable)
Mixture of stimulant and depressant effects: • Elevated mood, relaxation, increased appetite • Paranoia, depression, anxiety • Hypertension, tachycardia • **Analgesic, antiemetic, appetite stimulant and anti-spasticity properties**	• Anxiolytic, neuroprotective • **Anticonvulsant**, **analgesic**, antiemetic, **anti-inflammatory**

TIP The ratio of **CBD** (cannabidiol) to **THC** (tetrahydrocannabinol) in the plant influences the therapeutic effects.

Health Canada. *Information for Health care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids,* 2013. Available from Internet: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

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What is “Medical Cannabis”?

Medical cannabis is **NOT**:

- Dried plant products
- Smoked
- Dosed in grams
- Used to get “high”
- A single product/drug

Medical cannabis **IS**:

- Derived from the cannabis plant
- Ingested in oil
- Defined by the amount of THC and CBD in mg of oil
- A number of different products with different physiologic effects

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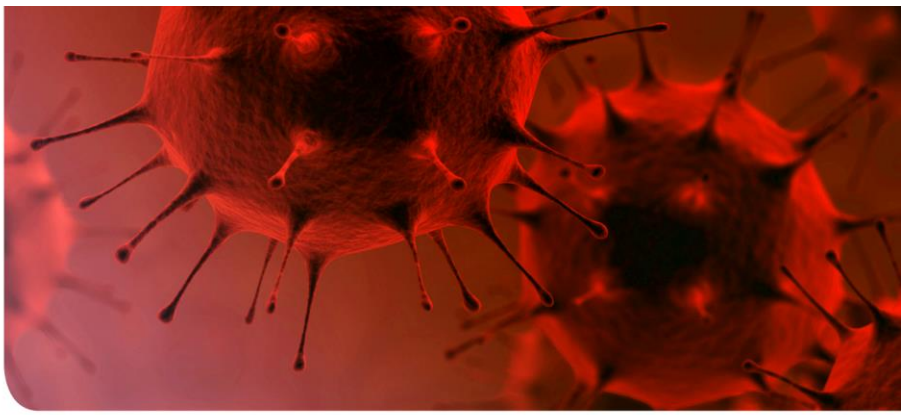

Endocannabinoid System and Pain

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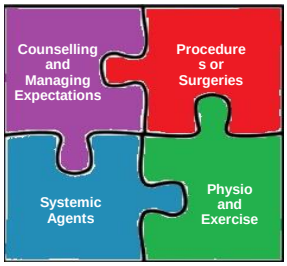
Chronic Pain (CP) in Clinical Practice

- **Problem for clinicians and patients**
  - 1/3 of adults will experience chronic pain
- **No new classes of medication to treat CP**
- **Opioids often relied upon to treat CP but…**
  - Harms most often limit long-term use
  - Patients don't like them
  - Limited data to support long-term or high-dose use
- **Patients want to be functional:**
  - Go to work
  - Basic activities of daily living
  - Family functions/social functions
- **Pain is a complicated physiologic process requiring a complex response**



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Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Canada: National Opioid Use Guideline Group (NOUGG); 2010 [2017, March 21]. Available from: http://nationalpaincentre.mcmaster.ca/opioid/

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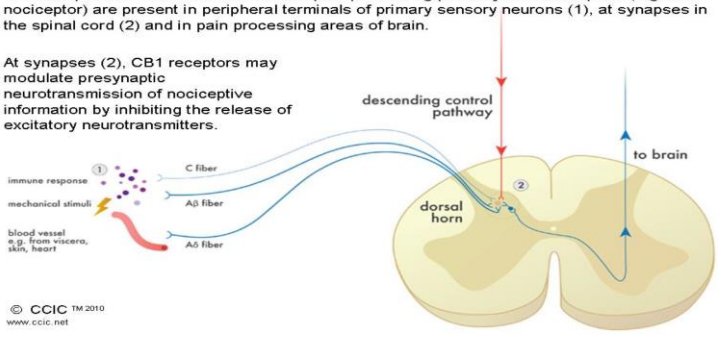
Cannabinoids and Pain Pathways

CB1 receptors are located in well-known pain processing pathways. The receptors (e.g. skin nociceptor) are present in peripheral terminals of primary sensory neurons (1), at synapses in the spinal cord (2) and in pain processing areas of brain.

At synapses (2), CB1 receptors may modulate presynaptic neurotransmission of nociceptive information by inhibiting the release of excitatory neurotransmitters.



Endocannabinoid system is a key endogenous system with modulatory actions at all stages of the pain processing pathways

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta analysis. *JAMA*.2015;313(24):2456-2473. Ware MA et al. *CMAJ*. 2010 Oct 5;182(14):E694-701
Aggarwal SK, Blinderman CD. Cannabis for symptom control #279. *J Palliat Med*. 2014;17:612–14.

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Endocannabinoid system and pain

Patients using cannabis report two phenomena:

1. Pain intensity decreases by approximately 3 points on VAS
2. Pain is present but does not seen to be bothered by it as much, unpleasantness is reduced, “I just don’t mind it as much and can ignore it”

- At the supraspinal level, the EC system can influence the affective/emotional aspects of pain sensation through actions in frontal–limbic circuits.
- Recent study using fMRI has confirmed cannabinoids ability to cause pain dissociation by causing reduced activity in the anterior cingulate cortex (ACC) and enhanced activity in the amygdala

IASP

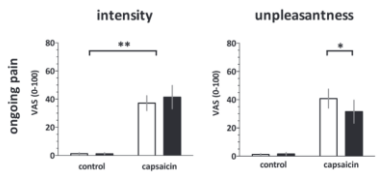
PAIN® 154 (2013) 124–134

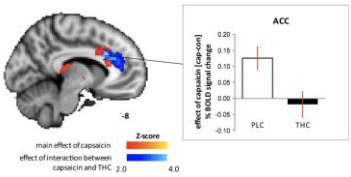
PAIN®

www.elsevier.com/locate/pain

Amygdala activity contributes to the dissociative effect of cannabis on pain perception

Michael C. Lee[a,d,*], Markus Ploner[a,b], Katja Wiech[a], Ulrike Bingel[a,c], Vishvarani Wanigasekera[a], Jonathan Brooks[a], David K. Menon[d], Irene Tracey[a]





Endocannabinoid system and pain

- While most research has focused on CB1 receptors, increasing interest is being turned towards CB2 receptors:
  - Mostly within immune cells in the periphery such as macrophages, lymphocytes, mast cells
  - Identification of CB2 receptors on immune cells in the CNS: astrocytes and microglia
  - Activation of CB2 is inhibitory and mediates the anti-inflammatory effects of the ECS and influences hyperalgesia in inflammatory pain states
- CB2 recently identified within the spinal cord
  - Central sensitization syndromes may have attenuation of CB2 upregulation within the CNS

Opioid Sparing Effects of Cannabinoids

- Cannabinoid and opioid receptors have similar signal transduction systems and expressed in brain regions involved in antinociception (periaqueductal gray, raphe nuclei, central medial thalamic nuclei)
- Mu-opioid receptors and CB1 receptors co-localize in the spinal cord at the first synaptic contact for peripheral nociceptive afferent neurons
- The antinociceptive effects of morphine are mediated predominantly by mu opioid receptors and may be enhanced by THC (CB1 and CB2 agonists)
- Cannabinoid antagonists have been shown to reverse the antinociception induced by morphine
- All of these discoveries of the endocannabinoid system and opioid receptors indicate shared mechanisms between both systems in regard to analgesia

Opioid Sparing Effects of Cannabinoids

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

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

- Clinically and pre-clinically cannabinoids exhibit analgesic effects and potentiate the anti-nociceptive effects of opioids
- Patients report an opioid reduction of 30% or more after being initiated on cannabinoids
- Safety: cannabinoid and opioid receptors do not generally co-localize in pathways associated with many of the side-effects associated with either drug alone
  - –Medullary control of respiration (OPI) & cerebellar effects (THC)
- Decreased opioid induced side effects and improvement in ADLs commonly experienced

- *Pre-clinical studies:*
  - *M*edian effective dose (ED50) of morphine administered in combination with delta-9-tetrahydrocannabinol (delta-9-THC) is 3.6 times lower (95% confidence interval (CI) 1.95, 6.76; n=6) than the ED50 of morphine alone. In addition
  - ED50 for codeine administered in combination with delta-9-THC was 9.5 times lower (95% CI 1.6, 57.5, n=2) than the ED50 of codeine alone

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Neuropathic Pain (Ware et al)

RESEARCH CMAJ

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

- Neuropathic pain of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia
- 23 cannabis naïve subjects
- Randomized, Double Blind, Placebo Cross-Over Design
- 2.5%, 6%, 9.4% THC or placebo
- Delivered as a single smoked inhalation 3 times daily
  - 4 – 14 day period – 5 days active, 9 days washout

Ware MA et al. *CMAJ*. 2010 Oct 5;182(14):E694-701

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Results – Ware et al

- **Primary outcome** – Pain intensity measured using an 11 point numeric rating scale

Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

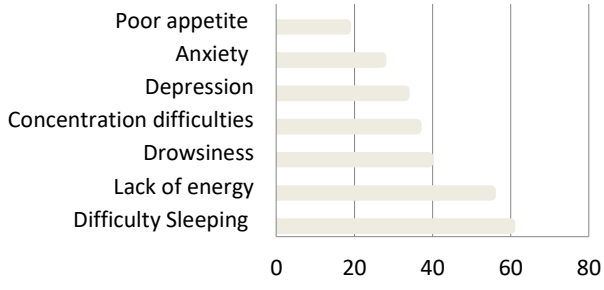
Potency, % of THC	Potency, % of THC, mean difference (95% CI)							
	0		2.5		6.0		9.4	
0	–	–	–	–	–	–	–	–
2.5	−0.13	(−0.83 to 0.56)	–	–	–	–	–	–
6.0	−0.09	(−0.78–0.60)	0.04	(−0.64 to 0.73)	–	–	–	–
9.4	−0.71	(−1.40 to −0.02)	−0.58	(−1.27 to 0.11)	−0.63	(−1.30 to 0.06)	–	–

Note: CI = confidence interval, THC = tetrahydrocannabinol.

- **Pre-Specified Secondary Outcomes**
  - Significant improvement in **sleep quality**
  - Significant improvement in **anxiety**

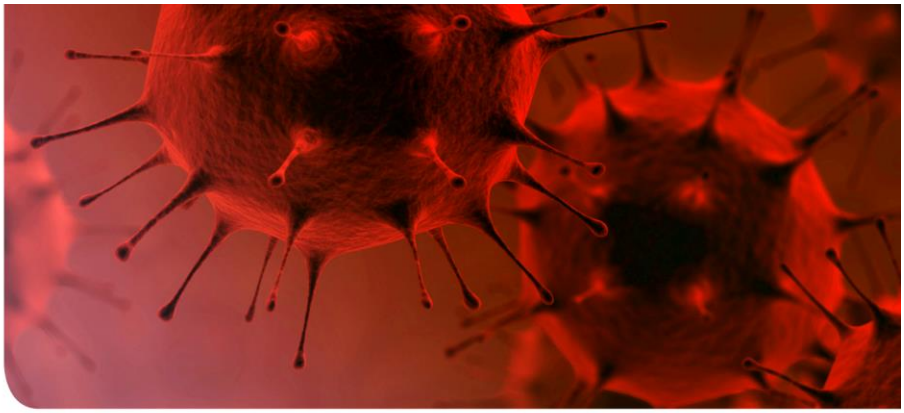
Ware MA et al. *CMAJ*. 2010 Oct 5;182(14):E694-701

Co-Morbidity Associated with Peripheral Neuropathic Pain



% patients with moderate to severe discomfort due to symptoms (N=126)

Adapted from Meyer-Rosberg K et al. Peripheral Neuropathic Pain - A Multidimensional burden for patients. *Eur J Pain* 2001; 5: 379-389



Cannabinoids as a treatment for Nausea and Vomiting

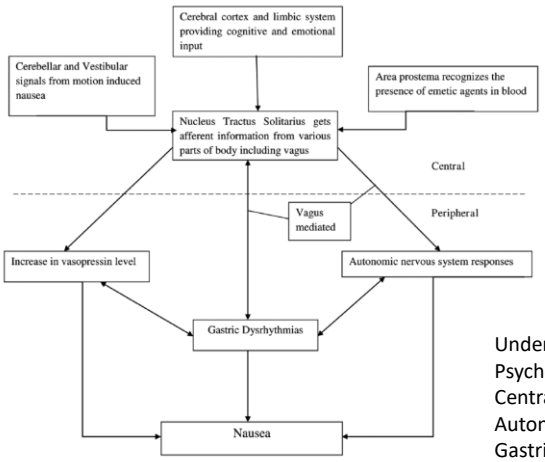
Nausea and vomiting

- Nausea is a commonly encountered symptom with a broad list of possible causes. It has been defined as an '**unpleasant painless subjective feeling that one will imminently vomit'** While nausea and vomiting are often thought to exist on a temporal continuum, this is not always the case. Thee are situations when severe nausea may be present with emesis and (less frequently) when emesis may be present without preceding nausea.
- Most individuals report that **nausea is more common, more disabling, feels worse and lasts longer than vomiting**. (Stern et al, 2011)

Chemotherapy induced nausea and vomiting

- The treatment of Chemotherapy Induced Nausea and Vomiting (CINV) has been revolutionized by the discovery of 5-hydroxytryptamines-3 receptor antagonists (5-HT3 antagonists) and Neurokinin 1 (NK1) receptor antagonists (ie: aprepitant) that suppress acute vomiting.
- 5-HT3 receptor antagonists less effective at suppressing acute nausea (18%) and ineffective in reducing delayed (>24 h) and anticipatory (conditioned) nausea and vomiting.
- Despite combo of 5-HT3 receptor antagonists, NK1 antagonists and steroids, these are still **ineffective in reducing acute and delayed nausea which are symptoms reported to be the most distressing to cancer patients undergoing chemotherapy**. None of these treatments are effective in reducing anticipatory nausea.
- Despite good therapies for vomiting, nausea (acute, delayed and anticipatory) continues to be a challenge for available pharmacotherapies. As many as 20% of patients discontinue treatment due to severity of nausea. This is also a condition that is under recognized.

Nausea



Underlying mechanisms involve:
Psychological states
Central nervous system
Autonomic nervous system
Gastric dysrhytmias

Endocannabinoid System Affects Susceptibility of Nausea and Vomiting

ECS acts to modulate nausea and vomiting in humans:

- Choukr et al. (2010) reported that motion sickness corresponded with lower blood endocannabinoid levels among participants undergoing parabolic flight maneuvers (PFs), whereas anandamide and 2-AG levels were higher among participants who did not experience motion sickness.
- CB1 receptor expression was reduced among participants experiencing motion sickness compared to those unaffected by PFs, who did not show any change in CB1 receptor expression from baseline values.

Nausea and the Endocannabinoid System

Underlying mechanisms involve:

- Psychological states → high concentration of cannabinoid receptors in limbic system
- Central nervous system → high concentration of cannabinoid receptors within CNS
- Autonomic nervous system → high concentration of cannabinoid receptors within ANS
- Gastric dysrhythmias → high concentration of cannabinoid receptors in GI tract and enteric nervous system

Understanding the function and distribution of the endocannabinoid system we are able to understand why cannabinoids are such an effective tool in controlling nausea when traditional therapies have failed. Cannabinoids are not a targeted therapy but have an effect on all mechanisms that may contribute to the development of nausea.

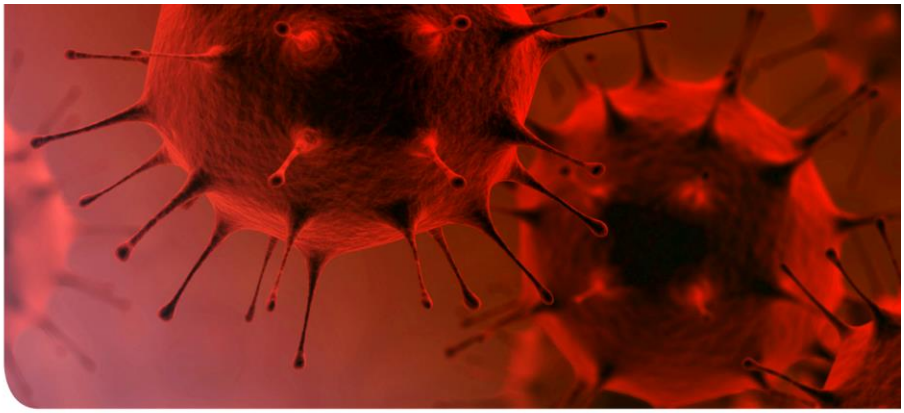
ECS and the GI System

- CB1 receptors in the myenteric plexus: **Inhibits contraction** by inhibition of acetylcholine release
- CB1 receptors in the submucosal plexus**: Inhibits secretion**
- CB1 receptors on peripheral nerve fibers within the brain-gut axis: Influence motility, secretion and **modules food intake and emesis**
- CB2 receptors may play a role in **intestinal inflammation** – upregulated in response to inflammatory insult

Cannabis and nausea/vomiting

Bottom Line

- Cannabis is not a first line treatment for chemotherapy induced nausea and vomiting or other gastrointestinal illnesses
- Can be considered after primary therapies have been tried
- May be more effective for nausea than traditional anti-emetics
- More research is needed for dosing
- Most research is looking at THC although THC and CBD is a reasonable starting point for most patients
- Cannabis hyperemesis syndrome is a rare but important syndrome to be aware of as it can be very debilitating. It is not seen in medical cannabis patients and most often seen in young, chronic recreational cannabis users.



How can cannabis be consumed?

PHARMACOKINETICS & MODES OF INGESTION

Plasma concentrations of THC and its metabolites following administration by inhalation (top) and oral ingestion (bottom)

	Onset of Action	Duration of Action	Psycho-activity
Inhaled (Vaporizer)	5-15 minutes	2-4 hours	+
Ingested (Oils)	1-2 hours	4-10 hours	++

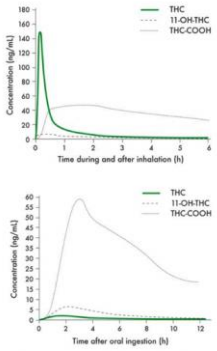
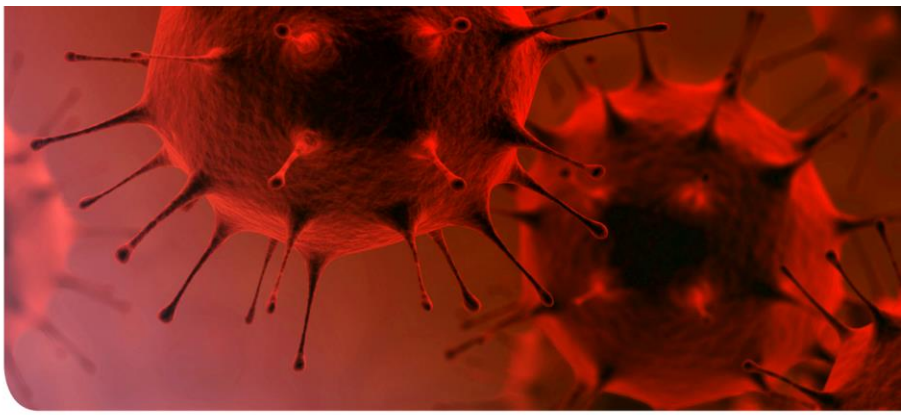


Image available at: http://www.ccic.net/picture/upload/Image/Poster/Slide8.JPG. Accessed April 1, 2018.

- Rapid absorption
- Preferred method for many
- We have an obligation to discourage the smoking of all plant substances
- Smoking one cannabis cigarette (“joint”) may cause as much lung damage as 5-9 tobacco cigarettes
- When combined with tobacco this increases addictive properties
- Not available in Australia

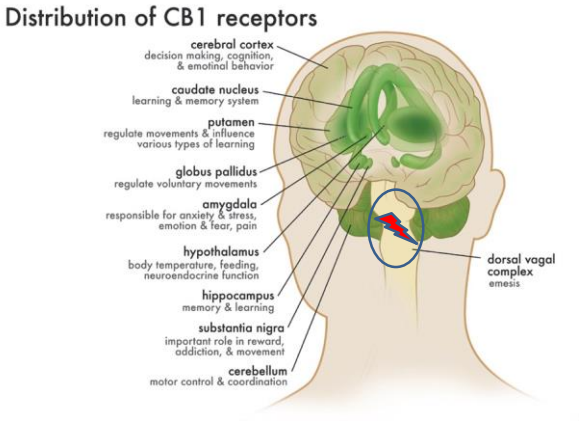
- Results in smaller quantity of toxic by-products such as carbon monoxide, polycyclic aromatic hydrocarbons (PAHs), and tar
- More efficient extraction of THC vs. smoking
- More rapid absorption
- Long-term effects unknown
- Various models: Tabletop, portable
- Dried flower not currently available in Australia
- Metered dose vaporizers for both dried cannabis flower and cannabis oil in development

- Slower onset of action and longer duration of action
- Lower T1/2 and predictable plasma levels
- Precise dosing and easy to titrate
- Less stigma/barriers to use
- Max THC concentration of 30 mg/mL, no max CBD concentration
- Variety of THC/CBD ratios and concentrations
- **START LOW, GO SLOW** to mitigate side effects
- Can be encapsulated for ease of use and incorporation into treatment regime



Safety, Toxicity and Adverse Events

45



Ref: www.CCIC.net

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Therapeutic Index

Cannabis 1000:1
Diazepam 100:1
Morphine 70:1
Cocaine 15:1
Alcohol 10:1
Digoxin 2:1

Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs.* 2000 Dec;60(6):1303-14. Review. PubMed PMID: 11152013.

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Acute Adverse Effects of Cannabis

- Any drug that crosses the blood-brain barrier can have adverse effects
- Cannabinoids are remarkedly benign in adverse effects compared to many other medications
- Very few absolute contraindications to cannabis use
  - There are a few groups where cannabis should be used cautiously

Notcutt WG, Clarke EL, eds. Cannabinoids in Clinical Practice: A UK Perspective. In: Handbook of Cannabis. Oxford, United Kingdom ; New York, NY: Oxford University Press; 2014:415-432.

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Acute Adverse Effects of Cannabis

Very Common	Common	Rare
• Dizziness • Drowsiness • Fatigue • Dry mouth • Cough, phlegm, bronchitis • Anxiety • Nausea • Cognitive effects	• Euphoria • Blurred vision • Headache	• Orthostatic hypotension • Psychosis/paranoia • Depression • Ataxia/dyscoordination • Tachycardia (after titration) • Cannabis hyperemesis • Diarrhea

MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med*. January 2018. doi:10.1016/j.ejim.2018.01.004 Notcutt WG, Clarke EL, eds. Cannabinoids in Clinical Practice: A UK Perspective. In: *Handbook of Cannabis*. Oxford, United Kingdom ; New York, NY: Oxford University Press; 2014:415-432.

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Mitigating Adverse Effects

- Most acute adverse effects are due:
  - Method of administration
  - Dosing of THC
- Mitigation of adverse effects
  - Starting at low dose
  - Titrating dose slowly
- Australia currently only allows oral format, which mitigates many of the respiratory effects

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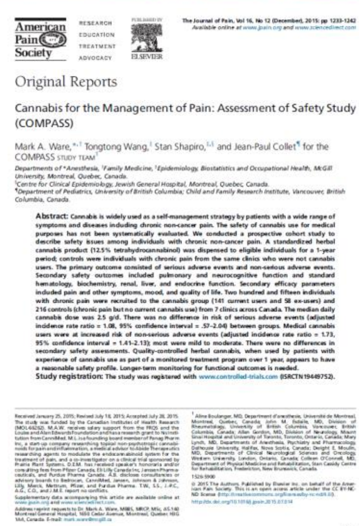
Chronic Adverse Effects

- Comparing adverse effects with medical cannabis in chronic pain (n=215)
- Medical cannabis versus non-users at pain clinic
- No difference in risk of serious adverse events (IR = 1.08, 95% CI= .57–2.04)
- Increased risk of non-serious adverse events (IR = 1.73, 95% CI 1.41–2.13); most are mild to moderate.


American Pain Society RESEARCH EDUCATION TREATMENT ADVOCACY
ELSEVIER
The Journal of Pain, Vol 16, No 12 (December), 2015: pp 1233-1242
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

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Departments of *Anesthesia, †Family Medicine, ‡Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada.
§Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada.
¶Department of Pediatrics, University of British Columbia; Child and Family Research Institute, Vancouver, British Columbia, Canada.

Abstract: Cannabis is widely used as a self-management strategy by patients with a wide range of symptoms and diseases including chronic non-cancer pain. The safety of cannabis use for medical purposes has not been systematically evaluated. We conducted a prospective cohort study to describe safety issues among individuals with chronic non-cancer pain. A standardized herbal cannabis product (12.5% tetrahydrocannabinol) was dispensed to eligible individuals for a 1-year period; controls were individuals with chronic pain from the same clinics who were not cannabis users. The primary outcome consisted of serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Secondary efficacy parameters included pain and other symptoms, mood, and quality of life. Two hundred and fifteen individuals with chronic pain were recruited to the cannabis group (141 current users and 58 ex-users) and 216 controls (chronic pain but no current cannabis use) from 7 clinics across Canada. The median daily cannabis dose was 2.5 g/d. There was no difference in risk of serious adverse events (adjusted incidence rate ratio = 1.08, 95% confidence interval = .57–2.04) between groups. Medical cannabis users were at increased risk of non-serious adverse events (adjusted incidence rate ratio = 1.73, 95% confidence interval = 1.41–2.13); most were mild to moderate. There were no differences in secondary safety assessments. Quality-controlled herbal cannabis, when used by patients with experience of cannabis use as part of a monitored treatment program over 1 year, appears to have a reasonable safety profile. Longer-term monitoring for functional outcomes is needed.
Study registration: The study was registered with www.controlled-trials.com (ISRCTN19449752).

Ware MA, Wang T, Shapiro S, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *The Journal of Pain*. 2015;16(12):1233-1242. doi:10.1016/j.jpain.2015.07.014

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Problematic Cannabis Use

- Regular use in recreational users can increase the risk of substance dependence:
  - Cannabis
  - Alcohol
  - Illicit drugs
- The earlier the person starts, the higher the risk
- Seems to be less of an issue in medical cannabis use

- Risk factors for cannabis use disorder
  - Depression
  - Male gender
  - Current tobacco use
  - Using illicit drugs
  - Poor school performance
  - Oppositional behaviours
  - Younger age of first alcohol use
  - Parental substance abuse
  - Antisocial behaviours
  - Childhood sexual abuse

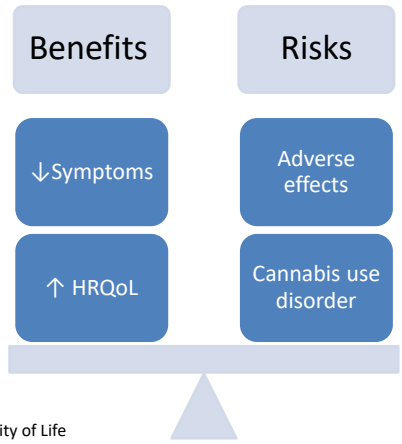
National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington (DC): National Academies Press (US); 2017. Hall W, Degenhardt L. The adverse health effects of chronic cannabis use. *Drug Test Anal*. 2014;6(1-2):39-45. doi:10.1002/dta.1506

Groups Where Cannabis Should be use With Caution

- People < 25 years of age
- Substance use disorder
- Schizophrenia, psychosis, unmanaged mental health disorder
- Unstable cardiac disease
- Unstable respiratory disease (if inhaled)
- Pregnancy and breastfeeding

Health Canada. Information for Health Care Professionals. [cited 2014 Nov 25]; Available from: http://www.hc-sc.gc.ca/dhp-mps/marijuana/med/infoprof-eng.php MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med [Internet]. 2018 Jan [cited 2018 Jan 12]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0953620518300049 Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The Pharmacologic and Clinical Effects of Medical Cannabis. Pharmacother J Hum Pharmacol Drug Ther. 2013;33(2):195–209. Greydanus DE, Hawver EK, Greydanus MM, Merrick J. Marijuana: Current Concepts. Front Public Health [Internet]. 2013 Oct 10 [cited 2014 Dec 10];1. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3859982/ Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. The Lancet. 2009 Oct 23;374(9698):1383–91.

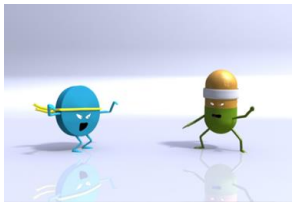
Balance of Benefits versus Possible Risk for the Specific Patient



HRQoL: Health-Related Quality of Life

METABOLISM AND DRUG INTERACTIONS

- Primarily hepatic through 2C9, 2C19, and 3A4
  - ↑ THC – with blockers fluoxetine, omeprazole, macrolides, ketoconazole, diltiazem, verapamil, HIV proteases, amiodarone
  - ↓ THC - 2C9, 3A4 stimulants (rifampicin, phenytoin, St. John's Wort)
- CYP isozyme polymorphisms affect the pharmacokinetics of THC
- Extensive drug interaction studies have not been done
- Existing studies have not demonstrated significant toxicity or loss of effect of concomitant medications but still theoretically possible



Health Canada's 2013 document *Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids.* Available at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php. *Accessed April 1, 2018.*

Take Home Points

- Cannabinoids represents a novel class of medication that can help with symptom management for a number of different conditions for individuals living with chronic illness
- While available in Australia, cannabis is not a first line treatment and should only be considered when other treatments have failed
- Despite a lack of high quality randomized controlled trials, cannabis is relatively safe, generally well tolerated with few clinical contra-indications
- Assessing a patient for cannabinoid medicine brings together the science and the art of clinical medicine

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