

# Medical Cannabis: How We Can Apply Our Knowledge for the Relief of Suffering



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## Today's **Highlights**

- 1. The United States of Norco**
2. Cannabis Cultural Context
3. Review of the Endocannabinoid System
4. Evidence for Select Conditions
5. Cannabis in Palliative Care
6. Cautions
7. Closing Thoughts

# An Opiate Outbreak

## Opiate prescribing over time:

1992 - 112 million Rx

2012 - 282 million Rx

2016 - 236 million Rx



According to the International Narcotics Control Board,  
in 1995 the US consumed 99.7% of the world's hydrocodone  
**\*6.2 billion pills in 2016**

## Last available data, 2016:

42,249 overdose deaths involving an opiate

115 opiate overdose deaths *daily*

# Thanks, Opiates

Opiates...

...can provide robust pain relief for those who suffer

...have revolutionized care for the seriously ill

...allow for pain-free transitions for the actively dying



# No Thanks, Opiates

Opiates...

...can be very sedating

...cause strong chemical dependence and sometimes addiction

...can cause severe constipation

...pose a risk for diversion and overdose



# Cannabis and Opiates

JAMA April 2018:

## **Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees**

- Comparing opiate prescription rates
- Nationwide, Medicaid recipients
- States with medical or adult use vs prohibition
- Legal implementation over 2011-2016

### **Results:**

5.88% lower opiate prescription rates with medical cannabis

6.38% lower with adult use cannabis

If 6% reduction in Rx results in 6% reduction in deaths in US...

**2,500 lives saved per year, 7 lives per day**

# Cannabis and Opiates

Second study, JAMA April 2018:

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

- Comparing filled “daily doses of opiates”
- Nationwide, Medicare Part D recipients
- States with medical, dispensary vs grow-your-own
- Legal implementation over 2010-2015

### **Results:**

16% fewer days opiate RX in states with medical dispensary  
8% reduction with home-cultivation-only

If 16% reduction in Rx results in 16% reduction in deaths in US...  
**6,800 lives saved per year, 18 lives per day**

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# Cannabis Prevalence

Most common “illicit drug” worldwide

- 147 million individuals annually, 2.5% of humans
- over 5 million daily users
- 22.2 million Americans annually prevalence
- 1 million monthly in US

# Attitudes

60% of Americans want full legalization  
88% for medical purposes

91% of US population already has some form of legal access

**Over 65% of medical school deans said that their graduates were “not at all prepared” to prescribe medical marijuana, and nearly 85% of residents and fellows say they received “no training in medical school or residency” on medical marijuana - *Drug and Alcohol Dependence, September 2017***



# Cannabis Cultural History



8000+ BCE – rope: hemp cord in pottery in Taiwan

6000 BCE – food: seeds and extracted oil for food in China

4000 BCE – clothing: hemp textiles in China and Turkestan

2737 BCE – **Medicine:** recorded by China Emperor Shen Neng

2000-800 BCE – prayer: Hindu text Atharvaveda, used ritually as offering to Shiva

100 BCE – paper: in China

1850 CE – entered US pharmacopoeia

1937 CE – Marijuana Tax Act banned MJ (Reefer Madness '36)

1970 CE – Controlled Substances Act

## Cultural Concerns / Structural Barriers

In USA, medical cannabis use more common among:

- white individuals, less among those of Asian, Latino, African American and immigrants
- likely because of prosecution differences, immigration fears
- employed individuals with health insurance and higher incomes
- CA residents making over \$60k most likely
- 65% are employed
- 73.4% have private insurance
  - cost barriers for the poor, ie recs, ID card, medication

## Cultural Concerns / Structural Barriers

- “Good people don't smoke marijuana” - Jeff Sessions
- ethnic Chinese in SF and moral corruption of children
- religious and moral objections about drug use
- concern about label as “junkie” or “stoner”
- legal status at federal level

### **Physician attitudes**

- 39% of specialist and 34% of PCP in Delaware “very unlikely” to authorize eligible patients for medical marijuana
- patients found to be unlikely to initiate conversation with PCP in anticipation of negative response

## Plants as Medicine

11% of the 252 drugs considered as basic and essential by the WHO were exclusively of flowering plant origin

Up to 50% the approved drugs during the last 30 years are from either directly or indirectly from natural products

# Morphine, codeine



Opium poppy, *Papaver somniferum*

Morphine marketed by Merck beginning in 1826

Opiates now nearing 1 prescription for every US man, woman, and child

# Aspirin



White Willow, *Salix alba*

Aspirin introduced by Bayer in 1899



# Atropine



Deadly Nightshade, *Atropa belladonna*

Atropine, scopolomine, and subsequent derivatives like tiotropium

# Paclitaxel



Pacific Yew, *Taxus brevifolia*

Paclitaxel Isolated in 1971, with Bristol-Meyers-Squibb gaining commercial approval in 1993

# Dronabinol



Cannabis, *Cannabis sativa*

THC/dronabinol/marinol, 1985 for chemotherapy-induced nausea and vomiting

## Extracts as Medicine

Listed in the US Pharmacopeia  
1850-1941

Extracts of marijuana and hashish  
were in the top 3 prescribed  
medications every year from 1842-  
1890s

Indications:

- neuralgia
- gout
- rheumatism
- tetanus
- hydrophobia
- epidemic cholera
- convulsions
- chorea
- hysteria
- depression
- DTs
- uterine hemorrhage



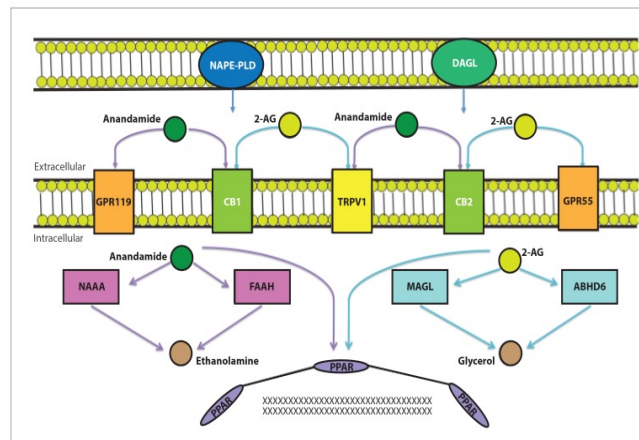
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## Endocannabinoid System

Has a homeostatic role, present in all vertebrates

“Eat, sleep, relax, forget, protect”



# Endocannabinoid System

Perhaps the most complicated and ubiquitous signaling system of the body

THC isolated in 1964

1988 CB1 receptor discovered

- similar density to dopamine, GABA, glutamate

Ligands:

**Anandamide (AEA)** from the Sanskrit *ananda* meaning "inner bliss"

**2-arachidonoylglycerol (2-AG)**

Endogenously present in even basic eukaryotes, including truffles and sea squirts – at least hundreds of millions of years of signaling evolution

# Endocannabinoid System

**CB1 –**

- THE most abundant G-protein coupled receptor
- responsible for appetite stimulation, perhaps both from gut AND brain
- a rat tasting dietary fats increases small intestine endocannabinoid levels

**CB2 –** mostly in immune system

**GPR55, GPR18, GPR119,** and transient potential ion-channels having similar action to capsaicin

**"non-classical receptors"** - in the gut, activated by pH or pressure, don't necessarily need a ligand

## Sites of Action

*\*affects nearly every major organ system\**

### CB1:

Brain  
Kidneys  
Liver  
Heart  
GI Tract  
Pancreas  
Adipose  
Muscle  
Reproductive  
organs  
Other?

### CB2:

Immune cells (T cells, B cells,  
monocytes)  
Spleen  
Tonsils  
Brain  
Heart  
Liver  
Lungs  
Other?

## Pharmaceuticals

Dronabinol (1985) – synthetic THC for chemotherapy-induced nausea and vomiting, indication expanded in 1992 for AIDS wasting syndrome

Nabilone (2006) – developed 1985, approved by FDA for CINV, but used widely in Canada and others as chronic pain adjunct (fibromyalgia, MS), palliative care

\*\*\* Most medical data is from these compounds, not the whole plant \*\*\*

Nabiximols – 1:1 plant-derived THC-CBD available in Europe and Canada, under investigation in US

## THC vs CBD

THC as most psychoactively potent of > 100 cannabinoids

CBD or cannabidiol thought to be more responsible for analgesic, antiinflammatory, antiseizure, ?antineoplastic effects and is not psychoactive

CBD strains and oils used more or less exclusively medically, no recreational purpose

Commercial testing available and widely used  
eg. strain that is 10% THC, 12% CBD

## Entourage Effect

Cannabinoids – over 100 of these terpenophenolic compounds  
Flavanoids  
Terpenes

**The idea that multiple compounds, working simultaneously in one or multiple systems, may have a stronger or more desirable effect, or fewer adverse effects, than one of those compounds alone.**

A particular type of “synergy,” *between* compounds within the same plant

Also potential for plant/pharmaceutical synergy:

e.g. Gallocatechins of green tea with antibiotics and curcuminoids of ginger with antineoplastics as potential co-mediations

CB receptor signaling modulates:

- pain and analgesia,
- inflammation,
- appetite,
- gastrointestinal motility,
- neuroprotection and neurodegeneration,
- immune cells,
- hormones, and other mood-altering neurotransmitters such as serotonin, dopamine, and glutamate.

1937 U.S. Congress passed the Marijuana Tax Act which criminalized the drug. In response Dr. William C. Woodward, testifying on behalf of the AMA, told Congress that,

"The American Medical Association knows of no evidence that marijuana is a dangerous drug" and warned that a prohibition "loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis."

“There just isn't any research out there”

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## Potentially Treatable with Cannabis

- Nausea and vomiting
- Neuropathic pain
- AIDS wasting
- Cancer-related pain
- Inflammatory bowel disease
- Pediatric seizures
- Anxiety, depression, PTSD, insomnia

## Oncology Considerations

Cannabis is the only antiemetic that is also an appetite stimulant

May prevent and treat chemo-induced peripheral neuropathy from vinca alkaloid, platinum, taxane agents (rodent models)

- only one clinical trial, of nabiximols
- placebo-controlled, 16 patients, 5 dropped > 2 points on visual-analog pain scale

Synergistic pain relief with opiates without pharmacokinetic interactions

Potential direct inhibition of cancer cell growth and proliferation

Consider: a single medication for nausea, anorexia, insomnia, depression, pain, rather than 6 meds with potential side effects

**\*Risk of internet testimonials leading patients to forgo treatment**

## Pediatric Seizures

### **CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience, Seizure, 2016**

- 74 patient cohort, age 1-18
- “resistant” epilepsy to > 7 antiepileptics
- 66% also failed ketogenic diet, Vagal stimulator, or both
- treated an average of 6 months
- 1 to 20mg/kg/d CBD

13(18%) reduced seizures by 75-100%  
25 (34%) 50-75% reduction  
9 (12%) 25-50% reduction  
10 (26%) <25% reduction

5 (7%) had aggravation  
5 (7%) other adverse events

## Chronic Non-cancer Pain

### **2011 Review Article in British Journal of Clinical Pharmacology**

- 22 RCTs, 4 not included, 18 met criteria
  - involved various cannabinoids, diseases, regimens
  - 766 participants
  - trial quality mean good at 6.1/7
- 
- 15 trials demonstrated significant analgesic effect
  - several also noted improvements with sleep
  - mean duration 3 weeks
  - few and mild side effects

## Chronic Non-cancer Pain

- 4 trials smoked cannabis with neuropathic pain – pos. effect
- 6/7 trials oromucosal extracts for neuropathic pain, rheumatoid arthritis showed positive results, with rheumatoid arthritis severity decreased by DAS28
- 4/4 nabilone for spinal pain, fibromyalgia, spasticity related pain, with comparable drop to dihydrocodeine
- 2/2 donabinol led to significant reduction in MS pain and mixed chronic pain
- THC-11-oic acid analog led to improvements in neuropathic pain with hyperalgesia and allodynia at 3 hours but normalized by 8 hours

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## Palliative Cannabis

November 22 1838, Sir WB O'Shaughnessy MD, first modern description of palliative cannabis (130mg extract per hour!)

...hydrophobia from rabies successfully treated and patient able to take some water, juice, rice, and sugarcane.

Eventually, the patient “sunk into a profound stupor, the breathing slightly stertorous...without further struggle, death terminated his sufferings at 4am”

## Palliative Research

Australia – Appetite stimulation and quality of life in CA

Israel

- Retrospective at University of Tel Aviv
  - 270 / 17,000 CA patients in one year
  - Of those alive and still using after a month, significant improvement in pain, well-being, appetite, nausea
  
- 131 Integrative Oncology patients, 8 week trial period
  - Improvements in all measured symptoms: nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, pain, **reduction in opiate use in almost half of patients**

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## Health and Safety Concerns

- unmasking mental health disorders
- impaired coordination
- impaired judgment
- dependence/addiction/abuse
- cannabis hyperemesis syndrome
- cannabis use disorder
- respiratory illnesses
- heart disease, especially in elderly, and if hypotension risk
- ?risk of stroke, ?risk of MI



# Systematic Review of Adverse Effects with Medical Use

Short term adverse events:

2008, systematic review of 40 years of research

- 321 articles with data on adverse effects
- 31 studies with data on medical use
- 23 randomized controlled trials
- 8 observational

4779 adverse events

- 4615 (96.6%) not serious
- dizziness 714 (15.5%)
- 164 serious adverse events
- MS relapse 21 (12.8%)
- vomiting 16 (9.8%)
- UTI 15 (9.1%)

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# Thoughts on Palliation

“Tending to dignity by way of the senses” - BJ Miller

When side effects become therapeutic

More to gain, less to lose

Safety



# Peace and Cannabis

It seems evident that at least one advantage was gained from the use of the remedy—the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases.... Next to cure, the physician will perhaps esteem the means which enable him “to strew the path to the tomb with flowers,” and to divest of its specific terrors the most dreadful malady to which mankind is exposed.

~ Sir O'Shaughnessy









## Dosing

Inhaled 2-5 min peak concentration, rapid decline, less conversion to liver

Oral peak at 2.5 hours, slow decline, metabolized to 11-hydroxy-THC by liver, ?more psychoactive than delta-9-THC

Sublingual concentrates: unknown kinetics

inhaled: better control of titration and effect  
oral: longer lasting, less potential negative health effects, harder to titrate

Self-titrated, and physician recommendation is not for a specific strain

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