Cannabinoids for Chronic Pain

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Financial Disclosures

- Dr. Jolene Smith is a paid consultant for Boston Scientific.
- Dr. Karry Smith is a paid consultant for MedPharm Iowa.

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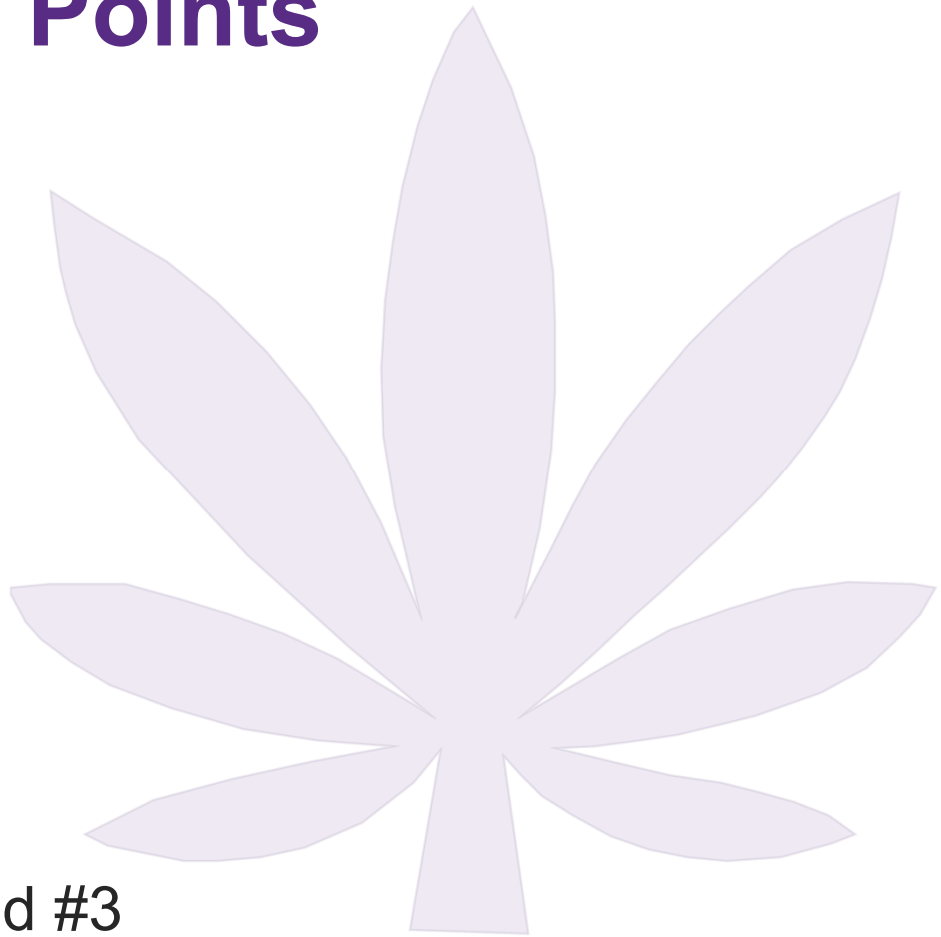
- The speakers will be discussing off-label use of some medications.

Discussion Points



- Case study #1
- Cannabinoids
- Pharmacology
- Dosing
- Safety
- Benefits for pain
- Iowa law
- Conclusions
- Case study #2 and #3

Case Study #1

- 34-year-old morbidly obese female and current smoker
- Currently on disability (not working)
- Chief complaint is widespread pain consistent with fibromyalgia
- Has noted side effects to Lyrica and Cymbalta and is only taking oxycodone
- Not willing to work toward weight loss
- History of methamphetamine use, but states has been clean for 6 years

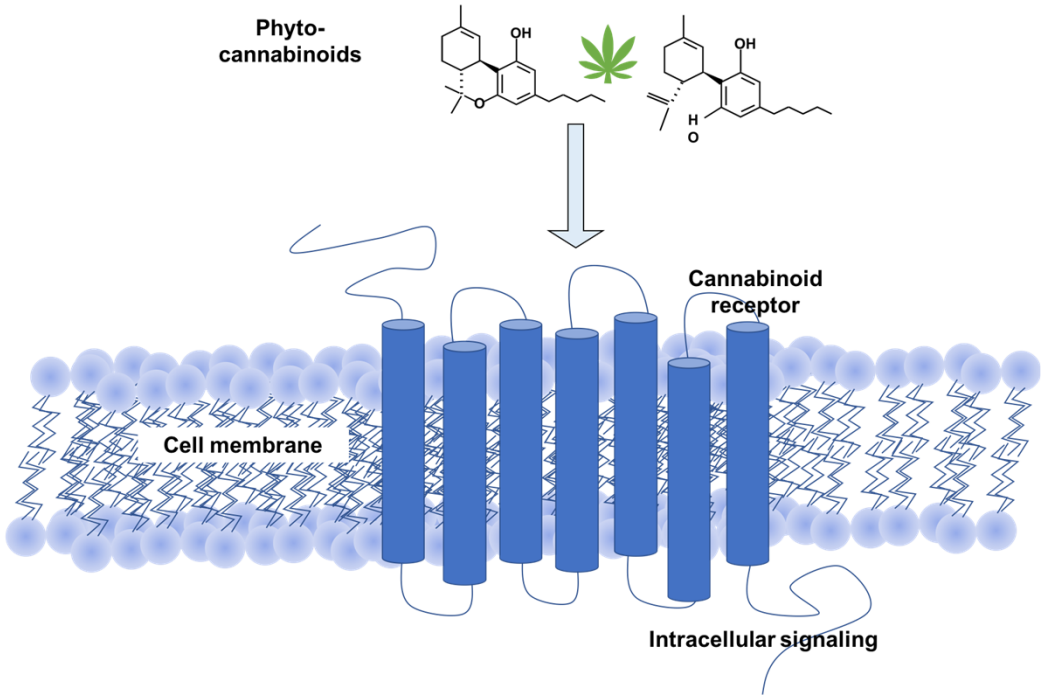
Cannabinoids

Cannabinoids

- Diverse class of chemical compounds that interact with cannabinoid receptors
- **Endo**cannabinoids are those produced by the human body (reviewed in Zou and Kumar, 2018)
  - Anandamide and 2-arachidonylglycerol
- **Phyto**-cannabinoids are plant-derived (reviewed in Hanus et al., 2016)
  - Includes Δ9-THC, CBD, others in the cannabis plant
- **Synthetic** cannabinoids are artificially manufactured (King, 2014; NIDA, 2018a)
  - A variety of chemical classes falls into this category
  - Marinol/dronabinol (synthetic THC) is manufactured synthetically, but same structure as THC
  - Some synthetic cannabinoids are sprayed onto herbal material and then called K2, Spice
    - **These synthetic compounds ARE NOT the same as THC or CBD and have different effects in the body**

Cannabinoid Receptors (CBRs)

- CB1 expressed in central nervous system (reviewed in Mackie, 2006 and in National Academies Press Report, 2017)
  - To lesser degree in peripheral nervous system, immune system, gastrointestinal system, liver
- CB2 expressed primarily in immune system (reviewed in Mackie, 2006 and in National Academies Press Report, 2017)
  - To lesser extent in central nervous system



Components of Cannabis, Including Phyto-Cannabinoids

Tetrahydrocannabinols (THCs)
Includes Δ9-THCA, the precursor of Δ9-THC that is found in the cannabis plant

Cannabidiols (CBDs)
Includes CBDA, the precursor of CBD that is found in the cannabis plant

Cannabigerols (CBGs)

Cannabivarins (CBVS)

> 500 natural compounds

Flavonoids, Lignans, Terpenes
Components of the cannabis plant, commonly found in other plants; are NOT cannabinoids

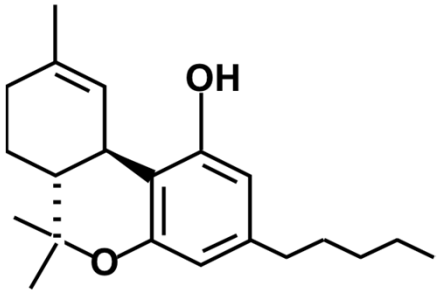
Cannabichromenes (CBCs), Others

Information reviewed in Hanus et al., 2016

Δ9-THC, Dronabinol, Marinol®, and Syndros®

Δ9-THC

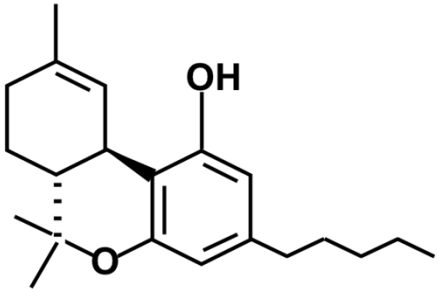
- Binds to CB1 and CB2 receptors
- Main psychoactive component of cannabis
- Schedule I substance per DEA (DEA, 2018)



Structure of Δ9-THC

Pharmaceutical versions of Δ9-THC

- Dronabinol has the same structure as Δ9-THC but is synthetic, not plant-derived (Marinol Label, 2017)
- Marinol and Syndros are FDA approved for:
  - Anorexia in patients with AIDS
  - Nausea and vomiting in patients undergoing chemotherapy

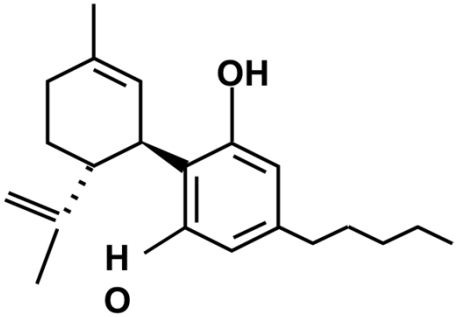


Structure of Dronabinol, Marinol, Syndros

CBD and Epidiolex®

CBD

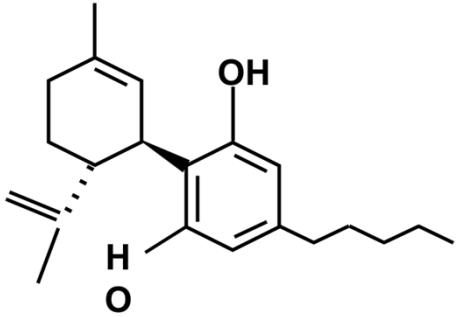
- Binds to CB1 (weak at best) and CB2 but has different effects than THC
  - Binds more weakly and possibly in a different place on the receptor
- Not psychoactive
- Schedule I substance



Structure of CBD

Epidiolex - pharmaceutical version of CBD

- Proprietary oral solution of **plant-derived** CBD (Epidiolex Label, 2018)
- FDA approved in June 2018
  - For treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome (Epidiolex Label, 2018)



Structure of Epidiolex

Cesamet® (Nabilone)

- Contains a synthetic ingredient ***similar*** to THC
- Formulation is capsules for oral administration
- FDA approved for treatment of the nausea and vomiting associated with cancer chemotherapy

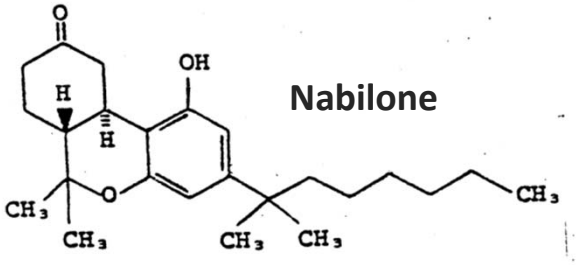
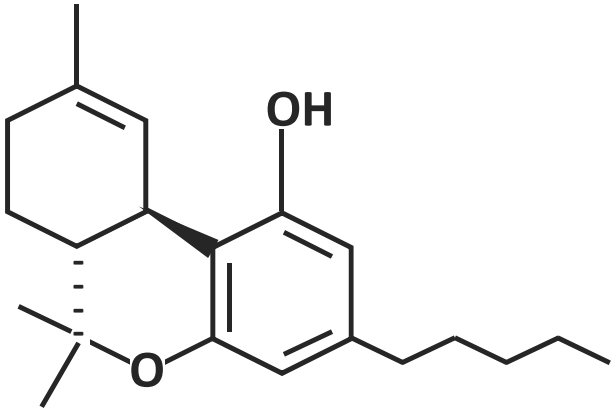


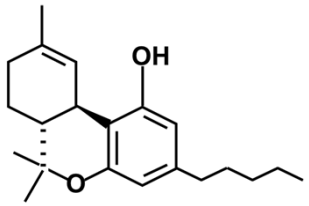
Image from Nabilone Label, 2006.



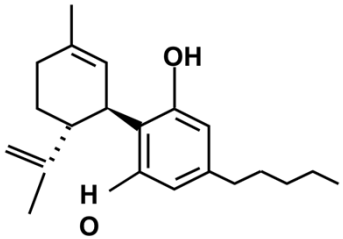
Structure of Δ9-THC

Sativex® (Nabiximols)

- Δ9-THC, CBD, specific minor cannabinoids, and other non-cannabinoid components (GW Pharma, 2018)
  - 1:1 ratio of THC:CBD
- **Plant-derived** extract, formulated as oral-mucosal spray
- Approved in 21 countries in Europe for treatment of spasticity associated with MS



Δ9-THC



CBD

+

Specific other cannabinoids and non-cannabinoids found in the cannabis plant (GW Pharma, 2018)

Pharmacology

Routes of Administration

- Sublingual, oral, inhalation (smoking or vaping), rectal, transdermal
- Inhalation after combustion (smoking) cannabis yields higher bioavailability of both THC and CBD than does oral administration
  - THC: 10-56% bioavailability smoking; ~6% oral (reviewed in WHO, 2018)
  - CBD: 31% bioavailability smoking; ~6% oral (reviewed in WHO, 2018)
    - Sublingual bioavailability of THC and CBD (based on studies of Sativex) is slightly higher than oral bioavailability (Karschner et al., 2011)
      - Peak plasma concentrations and time to peak plasma concentrations were not significantly different between sublingual and oral
- Route of administration is an important consideration when comparing studies

Pharmacokinetics of Δ9-THC

- Inhalation (reviewed in WHO, 2018)
  - Peak plasma levels 3-10 minutes after inhalation
  - Peak "high" 20-30 minutes after smoking
- Oral administration (reviewed in WHO, 2018)
  - First-pass metabolism in the liver
  - Estimated bioavailability is ~6% with considerable inter-patient variability
  - Peak plasma levels typically 60-120 minutes after ingestion
    - Delays of up to 4-6 hours have been reported
    - Absorption affected by food, individual variability
  - Plasma levels fall rapidly, whereas behavioral effects are prolonged, in comparison
    - May result from slow elimination from the brain
- *Pharmacokinetics of CBD similar to Δ9-THC (reviewed in WHO, 2018)*

Effects on Drug Metabolism

- **Metabolism of THC is predominantly hepatic**
  - **Cytochrome P450 (CYP 450) isozymes CYP2C9 and CYP3A4**
  - **THC is a CYP1A2 inducer**
- Inhibitors and inducers of CYP2C9 and CYP3A4: May alter THC systemic exposure (Marinol Label, 2017)
- Highly protein-bound drugs: Potential for displacement of other drugs from plasma proteins (Marinol Label, 2017)
- **See Marinol labeling for additional information**

- **Metabolism of CBD is hepatic** (reviewed in WHO CBD Report, 2018)
  - **Main isoforms involved are CYP3A4 and CYP2C19**
  - **Additional enzymes that metabolize CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5**
- Moderate or strong inhibitors of CYP3A4 or CYP2C19: Consider dose reduction of CBD (Epidiolex Label, 2018)
- Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 (eg, clobazam) (Epidiolex Label, 2018)
- Substrates of CYP1A2 and CYP2B6 may also require dose adjustment (Epidiolex Label, 2018)
- **See Epidiolex labeling for additional information**

Dosing

Dosing

- Iowa currently allows: capsules, extracts, concentrates, lotions, ointments and tinctures
- For oral administration, we can use information about dosing ranges of pharmaceutical versions of THC, CBD, and THC:CBD
- Per communication with experts, the advice is to 'start low and go slow' with THC
  - No safety concerns about CBD
  - Dr. Mark Ware believes 2.5 mg THC 2-3 times per day for an adult is a conservative starting point and can titrate up from there
  - This is in line with starting doses of pharmaceutical THC and Sativex

Dosing of Pharmaceuticals

Marinol (THC)

For chemotherapy-associated nausea

- Recommended starting dose (oral) is 5 mg/m^2, twice per day
  - Adult humans are ~1.5 to 2.0 m^2
  - Equates to total daily dose of 15 to 20 mg per day
- Titrate slowly
- Maximum dose is 15 mg/m^2, 4 to 6 times per day
  - Equates to total daily dose of up to 135 to 180 mg per day

Info from Marinol Label, 2017

Epidiolex (CBD)

For seizures associated with Lennox-Gastaut or Dravet syndromes

- Starting dose (Epidiolex; oral)
  - 2.5 mg/kg, twice daily (total of 5 mg/kg/day)
- Can increase after one week
- Maximum recommended maintenance dose
  - 10 mg/kg twice daily (total of 20 mg/kg/day)
- If extrapolated to a 70 kg adult, the maximum dose is 1400 mg per day

Info from Epidiolex Label, 2018

Dosing of Pharmaceuticals (Sativex)

For Multiple Sclerosis (Sativex)

- Starting dose (buccal) is 2 sprays per day
  - Each spray contains 2.7 mg THC, 2.5 mg CBD
  - Total of 5.4 mg THC and 5.0 mg CBD per day
- Titration of dosing is recommended
- Some patients may require more than 12 sprays
  - Note that some Sativex trials have allowed up to 48 sprays per day (patients with previous cannabis experience/use)
  - Total of 129.6 mg THC, 120 mg CBD per day

Dose titration schedule for Sativex[1]

Day	Number of sprays in the morning (between waking and midday)	Number of sprays in the evening (between 4pm and bedtime)	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Info from Sativex Monograph, 2015

Safety

Cannabis Adverse Effects

- Cannabis lifetime risk for dependence of 9% (Lopez-Quintero et al., 2011)
  - Compared to 67.5% for nicotine users, 22.7% for alcohol users, 20.9% for cocaine users
  - These were not medical cannabis users
  - One small study showed that transition to dependence happens more quickly for opioids than for alcohol, cocaine, tobacco, or cannabis (Ridenhour et al., 2006)
- Cannabinoid hyperemesis syndrome (long-term, heavy recreational cannabis users)
  - Average use time in one case series study was 16.3 ± 3.4 years (Abell et al., 1988)
  - Symptoms resolve when cannabis use stops (period of months)
- Cannabis (THC) overdose (Sativex Monograph, 2015)
  - Overdose severe enough to cause depression of consciousness should be treated with the normal precautions for dealing with an unconscious patient by securing the airway and monitoring vital signs
  - Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance
  - Benzodiazepines (5 to 10 mg diazepam *per oral)* may be used for treatment of extreme agitation

Short-Term Effects of Δ9-THC

- Δ9-THC can cause tachycardia shortly following administration (reviewed in WHO, 2018)
  - Patients with poorly controlled heart conditions are not good candidates for treatment
- Higher doses are associated with anxiety, panic, confusion, disorientation in some users
- Can provoke **transient** psychosis-like states in some healthy users (high doses)
  - Note that individuals with personal or first-degree family history of psychosis should be excluded from treatment
- Impaired attention, short-term memory
- Cognitive, psychomotor, perceptual alterations, generally lasting 3-8 hour depending on dose and route of administration (Hunault et al., 2014; reviewed in Savage et al., 2016)
- Causes driving impairment in both on-road and simulator tests (reviewed in WHO, 2018)
  - Dose-dependent effects
  - Observed in both occasional and heavy users of cannabis

Typical Side Effects of Cannabinoids Observed In Clinical Trials

- Summary of 79 RCTs for various indications (6462 participants)
  - Studies available through April 2015
  - Studies included smoked cannabis, THC (Marinol/dronabinol), Sativex (nabiximols), Cesamet (nabilone), a synthetic cannabidiol
- Cannabinoids are associated with increased risk of short-term AEs, SAEs, withdrawal from treatment due to AEs
  - The most common individual AEs experienced are shown and fall into dizziness, dry mouth, drowsiness/fatigue

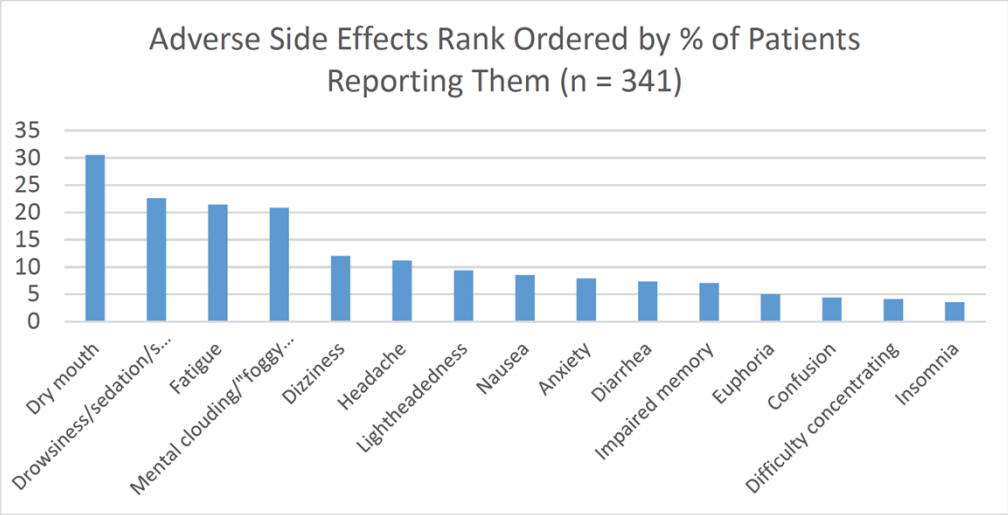
Individual AEs	No. of Studies (No. of Patients)	Summary OR (95% CI)
Dizziness	41 (4243)	5.09 (4.10-6.32)
Dry mouth	36 (4181)	3.50 (2.58-4.75)
Nausea	30 (3579)	2.08 (1.63-2.65)
Fatigue	20 (2717)	2.00 (1.54-2.62)
Somnolence	26 (3168)	2.83 (2.05-3.91)
Euphoria	27 (2420)	4.08 (2.18-7.64)
Depression	15 (2353)	1.32 (0.87-2.01)
Vomiting	17 (2191)	1.67 (1.13-2.47)
Diarrhea	17 (2077)	1.65 (1.04-2.62)
Disorientation	12 (1736)	5.41 (2.61-11.19)
Asthenia	15 (1717)	2.03 (1.35-3.06)
Drowsiness	18 (1272)	3.68 (2.24-6.01)
Anxiety	12 (1242)	1.98 (0.73-5.35)
Confusion	13 (1160)	4.03 (2.05-7.97)
Balance	6 (920)	2.62 (1.12-4.68)
Hallucination	10 (898)	2.19 (1.02-4.68)
Dyspnea	4 (375)	0.83 (0.26-2.63)
Paranoia	4 (492)	2.05 (0.42-10.10)
Psychosis	2 (37)	1.09 (0.07-16.35)
Seizures	2 (42)	0.91 (0.05-15.66)

Whiting et al., 2015

Side Effects Reported by Minnesota Patients With Intractable Pain

- Minnesota allows oil, capsule, topical, vaporizable oils
- Varying THC:CBD ratios
- Side effects in medical cannabis program who qualify under intractable pain
  - 341 submitted reports of adverse effects

Figure 6.1. Top 15 most commonly reported adverse side effects represented by the percentage of patients reporting them (out of 341 patients).



Info from Minnesota Intractable Pain Report, 2016

Summary of THC/Cannabis Safety

- Adverse events most commonly reported include dizziness, dry mouth, drowsiness/fatigue, nausea/vomiting (Whiting et al., 2015)
- A 3-year trial of up to 28 mg THC per day in patients with MS revealed no new safety concerns beyond the known safety profile (Ball et al., 2015)
- A 1-year trial in which median THC use was 312.5 mg per day found no increased risk of SAEs in the medical cannabis group; there was increased risk for non-serious AEs (Ware et al., 2015)
  - Cannabis users did experience reduction in pain
- Contraindications for cannabinoid use include poorly controlled heart conditions, history of certain psychiatric problems, substance abuse, pregnancy/breastfeeding
- Additional information, including specific warnings, is available in the Marinol, Epidiolex, and Sativex labeling

Benefits

Whiting et al., 2015 (Systematic Review)

- Whiting et al conclude that **there [is] moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain**

  - Cannabinoids in the form of smoked THC or Sativex (buccal spray)
  - Chronic pain was assessed in 28 studies (63 reports; 2454 participants) (Whiting et al., 2015 [systematic review and meta analysis])
    - The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (OR, 1.41 [95% CI, 0.99-2.00]; 8 trials
  - Used a standardized approach to determine the quality of studies included in the systematic review

National Academies Report, 2017 (Systematic Review)

- **"There is substantial evidence that cannabis is an effective treatment for chronic pain in adults."** (National Academies Press Report, 2017)
  - Important to note that cannabis contains both THC and CBD
  - The majority of the studies included in the analysis by the National Academies of Science, Engineering, and Medicine were also included in the systematic review and meta-analysis by Whiting et al., 2015
    - NAP report included an additional 2 studies (Wilsey et al., 2016; Wallace et al., 2015)

Clinical Reviews Conclude There is Evidence For a Benefit in Treating Pain

- Hill et al., 2017 (clinical review)
  - **"…there is converging evidence to support the notion that cannabis can produce acute pain-inhibitory effects among individuals with chronic pain."**

- Hill, 2015 (clinical review)
  - **"…chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis are the indications for medical marijuana supported by high-quality evidence…"**

Data from Minnesota (Patients With Intractable Pain)

- August 1 - December 31, 2016 a total of 2245 patients were enrolled in the program for the first time in this interval under the qualifying condition of intractable pain
  - Most common causes were **axial** (mechanical, localized) **back pain** (23%), **radicular** (nerve, extends into legs) **back pain** (14%), **fibromyalgia/myofascial pain** (10%), **neuropathy** (8%), and **osteoarthritis** (7%)
  - Survey response rates: patient (54%) and health care practitioner (40%)
- High level of benefit reported by 61% patients and 43% healthcare practitioners (score of 6 or 7 on a seven-point scale)
  - Little or no benefit reported by 10% patients and 24% of health care practitioners (score of 1, 2, or 3 on seven-point scale)
  - Reduction in pain severity most commonly reported benefit (64%)

Info from Minnesota Intractable Pain Report, 2016

Summary of Benefits

- It is widely accepted that cannabis has efficacy for pain
  - The systematic reviews/clinical reviews presented here all reach the same basic conclusion
- Patients and healthcare providers both report reduction in pain as a benefit (Minnesota)
- Expert opinion
  - Dr. Mark Wallace (UCSD) and Dr. Mark Ware (Canada) both currently use cannabinoids to treat patients with chronic pain in their practices
  - Substantial benefit for many patients with pain
  - Anecdotal evidence, survey data, and associative studies show a possible link between cannabinoid therapy and reduction of pain medication use

Iowa Law

Qualifying Conditions in Iowa

- **Cancer – With severe or chronic pain**, nausea or severe vomiting, cachexia or severe wasting.
- Seizures
- Crohn's disease
- **Untreatable pain**
- Multiple Sclerosis with severe and persistent muscle spasms
- AIDS or HIV (as defined in Iowa Code, section 141A.1)
- Amyotrophic lateral sclerosis (ALS)
- Parkinson's disease
- Any **terminal illness** with a probable life expectancy of under one year – if the illness or its treatment produces one or more of the following: **severe or chronic pain**, nausea or severe vomiting, cachexia or severe wasting

Info from Iowa Department of Public Health, 2018

Iowa Definition of Pain

- Iowa House File 524: “Untreatable pain” means any pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities appropriate for the patient has been used without adequate result or with intolerable side effects.

- *Note than severe or chronic pain associated with **cancer** or **terminal illness** are separate qualifying conditions*

Info from Iowa House File 524, 2017

Conclusions

- FDA-approved cannabinoid medications are currently available
  - dronabinol (Marinol/Syndros), nabilone (Cesamet), Epidiolex
- Cannabinoids show efficacy in treating pain in some patients
  - Particularly THC in combination with CBD
  - Some patients report a reduction in their other pain medications, including opioids
- Some of the more common side effects observed in trials of cannabis include dizziness, dry mouth, drowsiness
- There are contraindications for treatment with cannabinoids, in particular THC, that include heart conditions, history of certain psychological problems, substance abuse, and pregnancy/breastfeeding
- Other risks include dependence, cannabinoid hyperemesis syndrome, THC overdose
- Untreatable pain and pain associated with cancer or terminal illness are qualifying conditions under the Medical Cannabidiol Act (Iowa)

Case Study #2

- 60-year-old female
- Main pain complaint is thoracic and low back pain and 3-4 occipital neuralgia headaches per week
- History of post-laminectomy syndrome and occipital neuralgia
- 18+ years of pain
- Has tried multiple rounds of physical therapy
- Medications tried include gabapentin, Lyrica, standard anti-inflammatories, SNRIs, opioids (methadone, hydromorphone, hydrocodone, oxycodone)
  - Has had spinal cord stimulator implanted and occipital nerve stimulator implanted
    - All explanted due to lack of efficacy
  - Has been on disability for many years
- Despite treatment, continues to have daily rated pain 8/10

Case Study #3

- 48-year-old male
- Injured elbow at work, which subsequently led to transposition of the ulnar nerve and resulted in complex regional pain syndrome (CRPS)
- Multimodal medications tried include gabapentin, Lyrica, muscle relaxants, anti-inflammatories, opioids
- Underwent stellate ganglion block, desensitization therapy, physical therapy, spinal cord stimulator
  - Spinal cord stimulator currently implanted and patient is using it but with ongoing pain
- Patient continues to work, no longer on opioids, pain 6/10 daily

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Opioids and Cannabis/Cannabidiol

Reduction in Opioid Prescriptions

- Two studies recently published in *JAMA Internal Medicine* highlight an association between legal cannabis/medical cannabis and reduction in opioid prescriptions (Bradford et al., 2018; Wen and Hockenberry, 2018)

Bradford et al., 2018

- Prescriptions for all opioids decreased by 3.742 million daily doses per year when medical cannabis dispensaries opened

Wen and Hockenberry, 2018

- ~5% decrease in **all** Medicaid-covered opioid prescriptions in states with medical cannabis laws
  - ~5% decrease in Schedule II opioid prescriptions
  - ~10% decrease in Schedule III/IV opioid prescriptions

Reduction in Pain Medication Use (Minnesota Patients With Intractable Pain)

- Over the past 6 months has this patient's use of medical cannabis assisted in reducing dosage or eliminating other medications used for pain? (Note: survey completed by healthcare provider).
  - **Of 568 complete reports, 340 (58.0%) indicated a reduction of pain medication**
    - The remainder indicated no reduction in pain medication use
  - **221 (37.7%) of these reports indicated a reduction in opioid use**
    - **127/221 were reported as reducing at least one opioid by 50% or more**

Info from Minnesota Intractable Pain Report, 2016

Expert Opinion – Concurrent Opioids

- Currently in the Canadian Guidelines for Neuropathic Pain, cannabinoids are a third-line treatment (Moulin et al., 2014)
  - Behind gabepentoids/tricyclics/SSRIs and opioids
  - These guidelines are 4 years old
- According to Mark Ware (McGill), MD, physicians are currently reconsidering whether cannabinoids should be first- or second-line (communication with Mark Ware (McGill), 2018)
  - Cannabinoids have a far better safety profile than opioids
- Dr. Mark Wallace (UCSD) also believes cannabinoids should be considered before opioids (communication with Mark Wallace, 2018; Melville, 2018)
- Dr. Ware does have patients on concurrent opioids and cannabinoids (communication with Mark Ware (McGill), 2018)
  - Ok with co-administration if can use the cannabinoids to keep the opioid dose down or eliminate it altogether
- Dr. Mark Wallace (UCSD) is also ok with having patients on concurrent cannabinoids and opioids, if patients have been compliant with opioid taper but are unable to come off opioids entirely due to increased pain and decreased quality of life and cannabinoids keep the opioid dose down (Melville, 2018)

Additional Safety Info

Safety Information From Marinol (Dronabinol/THC) Label

- Neuropsychiatric adverse reactions
  - May cause psychiatric and cognitive effects and impair mental and/or physical abilities. Avoid use in patients with a psychiatric history.
  - Inform patients not to operate motor vehicles or other dangerous machinery until they are reasonably certain that MARINOL does not affect them adversely.
- Hemodynamic instability
  - Patients with cardiac disorders may experience hypotension, hypertension, syncope or tachycardia. Avoid concomitant use of drugs with similar effect
- Seizures and seizure-like activity
  - Weigh the potential risk versus benefits before prescribing MARINOL to patients with a history of seizures, including those requiring anti-epileptic medication or with other factors that lower the seizure threshold. Monitor patients and discontinue if seizures occur.
- Multiple substance abuse
  - Assess risk for abuse or misuse in patients with a history of substance abuse or dependence, prior to prescribing MARINOL and monitor for the development of associated behaviors or conditions.
- Paradoxical nausea, vomiting, or abdominal pain
  - Consider dose reduction or discontinuation, if worsening of symptoms while on treatment.

Marinol Label, 2017

Safety Information From Epidiolex (CBD) Label

- **Generally well tolerated with good safety**
- To date, no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD (reviewed in WHO CBD Report, 2018)
- **No abuse liability** (Babalonis et al., 2017; reviewed in WHO CBD Report, 2018)
- Most common AEs (10% or more) in Epidiolex trials were (Epidiolex Label, 2018)
  - Somnolence
  - Decreased appetite
  - Diarrhea
  - Transaminase elevations
  - Fatigue, malaise, asthenia
  - Rash
  - Insomnia, sleep disorder, poor quality sleep
  - Infections

Warnings (Epidiolex Label, 2018)

- Hepatocellular injury
  - Transaminase elevations
  - Concomitant use of valproate increases this risk
- Somnolence and sedation
  - Monitor and advise patients not to drive or operate machinery until they have gained sufficient experience on treatment
- Suicidal behavior and ideation
- Hypersensitivity
  - Seek immediate care
- Withdrawal of anti-epileptics
  - CBD should be withdrawn slowly to minimize risk of increased seizure frequency

Summary of CBD and THC:CBD (Sativex) Safety

- CBD has a very favorable safety profile (communication with Mark Ware, 2018; communication with Mark Wallace, 2018)
  - No risk for abuse, dependence (WHO CBD Report, 2018)
- Maximum approved dose for Epidiolex (CBD) extrapolated to a 70 kg adult is 1400 mg per day
- Most common AEs in clinical trials included (Epidiolex Label, 2018):
  - Somnolence
  - Decreased appetite
  - Diarrhea
  - Transaminase elevations
- THC:CBD (Sativex) includes both THC and CBD, so the safety profile has components of both
  - In a registry study >1 year, no indications of abuse, dependence, or diversion of Sativex (Etges et al., 2016)
- In all placebo-controlled trials in MS, adverse events have usually been mild or moderate in severity (Sativex Monograph, 2015)
- In most patients, adverse events resolved without treatment, and some on a reduction of dosage (Sativex Monograph, 2015)

Additional Benefits/Pain Info

Primary Research Studies Find Benefit for Pain

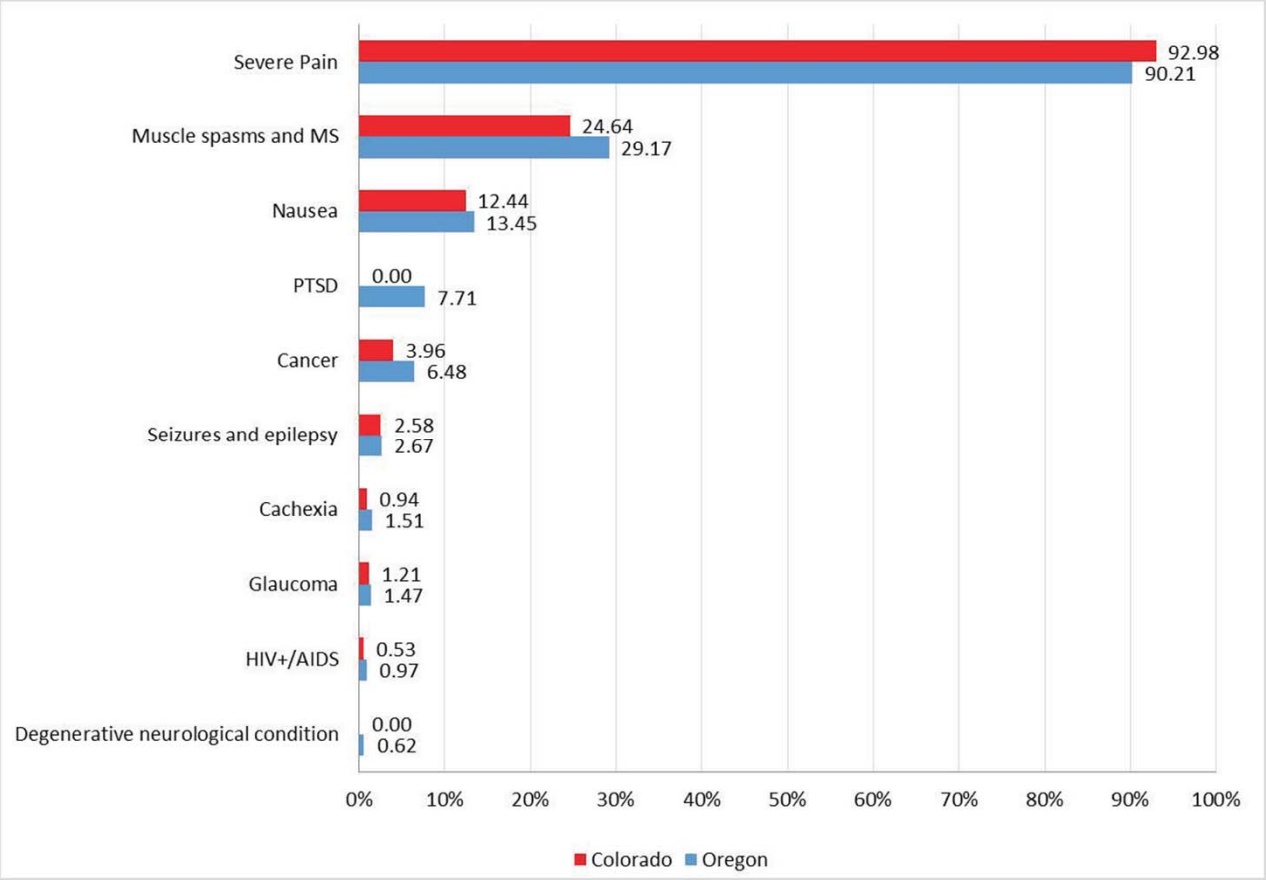
Wallace et al., 2015 (primary research)

- **Dose-dependent reduction in diabetic peripheral neuropathy spontaneous pain ratings**
  - Randomized, double-blind, placebo-controlled trial
  - Inhaled cannabis (varying THC content) for diabetic neuropathy
    - Low (1%), medium (3.5%), or high (7%) THC
    - Assessed for measures of pain over 4 hours

Wilsey et al., 2016 (primary research)

- **Cannabis reduced neuropathic pain scale ratings**
  - Randomized, placebo-controlled, crossover trial
    - Placebo, 6.7% THC, or 2.9% THC
  - Vaporized cannabis in 42 patients with central neuropathic pain related to spinal cord injury and disease
  - 2 administrations in 4 hour period
  - The mean vaporized was 45.9 mg (29.9–83.8 mg) during the 2.9% THC sessions and 56.3 mg (15.7–172.9 mg) during the 6.7% THC sessions

Percentage of Medical Cannabis Patients Reported by Condition in Colorado and Oregon, July 2016



Info from National Academies Press Report, 2017

Minnesota Definition of Pain

- Minnesota Statute 152.125: For purposes of this section, "**intractable** pain" means a pain state in which the cause of the pain cannot be removed or **otherwise treated with the consent of the patient** and in which, in the generally accepted course of medical practice, **no relief or cure of the cause of the pain is possible, or none has been found after reasonable efforts**. Reasonable efforts for relieving or curing the cause of the pain may be determined on the basis of, but are not limited to, the following: *(emphasis mine)*
  - (1) when treating a nonterminally ill patient for intractable pain, evaluation by the attending physician and one or more physicians specializing in pain medicine or the treatment of the area, system, or organ of the body perceived as the source of the pain; or
  - (2) when treating a terminally ill patient, evaluation by the attending physician who does so in accordance with the level of care, skill, and treatment that would be recognized by a reasonably prudent physician under similar conditions and circumstances.

Info from Minnesota Statute 152.125

Contrasting the Definitions of Pain

- Minnesota: “intractable”
  - Hard to control or deal with
- Iowa: “untreatable”
  - No medical care is available or possible
- The Iowa definition is nebulous
  - What does “the full range of pain management modalities” actually mean?
  - Absence of a patient consent clause
    - What if a patient does not wish to undergo a certain treatment (for example, be placed on opioids) – does this disqualify them from certification of a qualifying condition?
- Pain will be one of the most common reasons that patients seek certification, and physicians need a clear definition in the Iowa law