Cannabinoids in Practice:
A Focus on Pain, Spasticity, and Policy

Jolene Smith, DO, DABA, DABA-PM

Iowa Physical Medicine & Rehabilitation Conference

Des Moines University

19 October 2018

Financial Disclosures

- Dr. Jolene Smith is a paid consultant for Boston Scientific and Abbott/St. Jude.
- Dr. Smith's spouse is a paid consultant for MedPharm Iowa.

Off-Label Use

- Dr. Smith will be discussing the off-label use of some medications.

Disclaimers

- Possessing, distributing, selling, or using cannabis is a federal crime. The information provided in this presentation is not intended to offer guidance or assistance in complying and/or violating federal law and this presentation is not meant to condone or promote illegal activities. Additionally, the speakers offer no advice concerning federal, state, or local consequences of engaging in any business in the medical cannabis/cannabidiol industry.
- The opinions presented here are the speakers' own and do not necessarily represent the opinions of their employers or any other entity with which the speakers have a relationship. The purpose of this presentation is to provide information on the uses of cannabinoids and all data and information provided is for educational purposes only and should not be considered medical or legal advice.
- This information is for educational purposes only. Providers managing patients who are using medical cannabis should refer to the research literature, state and federal law, accepted medical guidelines and position statements, and their own clinical judgement to inform medical decisions. This information is not a substitute for independent medical judgement of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The speakers are not responsible for and have no liability for any medical decision made (or medical outcome that occurs) based on information presented here.
- While every effort has been made to ensure the accuracy and completeness of the information contained herein, the speakers assume no legal liability for the completeness or usefulness of any information disclosed and accept no liability for any loss or damages howsoever arising. The speakers reserve the right to make changes to any information included within this presentation at any time and are not responsible for the content of any website or article referenced in this presentation.

Discussion Points

- Case study #1
- Cannabinoids
- Pharmacology
- Dosing
- Safety
- Benefits for pain
- Benefits for multiple sclerosis
  - Central pain and painful spasms
  - Spasticity due to spinal cord injury
- Iowa law
- Conclusions
- Resources for developing practice policies
- Case study #2 and #3

Case Study #1

- 31-year-old morbidly obese female and current smoker
- Currently not working (on disability)
- Chief complaint is widespread pain consistent with fibromyalgia
- Has noted side effects to Lyrica and Cymbalta
  - Is taking oxycodone
- Unwilling to work toward weight loss
- History of methamphetamine use, but states has been clean for 7 years

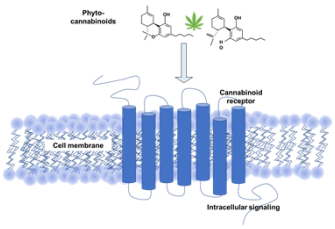
Cannabinoids

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 ∆9-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)

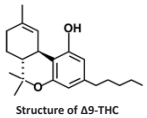
- CB1 expressed in central nervous system (reviewed in Mackie, 2006 and in National Academies Press Report, 2017)
  - To lesser degree in peripheral nervous system, immune system, gastrointestinal system, liver
- CB2 expressed primarily in immune system (reviewed in Mackie, 2006 and in National Academies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



∆9-THC, Dronabinol, Marinol®, and Syndros®

∆9-THC

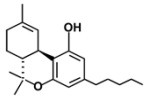
- Binds to CB1 and CB2 receptors
- Main psychoactive component of cannabis
- Schedule I substance per DEA (DEA, 2018)



Structure of ∆9-THC

Pharmaceutical versions of ∆9-THC

- Dronabinol has the same structure as ∆9-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

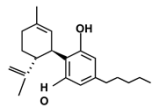


Structure of Dronabinol, Marinol, Syndros

CBD and Epidiolex®

CBD

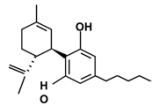
- Binds to CB1 (weak at best) and CB2 but has different effects than THC
  - Binds more weakly and possibly in a different place on the receptor
- Not psychoactive
- Schedule I substance



Structure of CBD

Epidiolex - pharmaceutical version of CBD

- Proprietary oral solution of **plant-derived** CBD (Epidiolex Label, 2018)
- FDA approved in June 2018
  - DEA rescheduled to Schedule V
  - 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

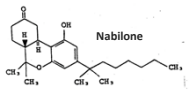
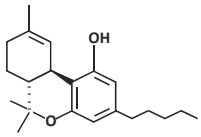


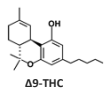
Image from Nabilone Label, 2006.



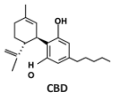
Structure of Δ9-THC

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 UK, European Union, Canada, Israel 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: oral forms (tablets, capsules, liquids, tinctures, sublingual); topical forms; nebulizable forms; suppositories
- 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

Info from Sativex Monograph, 2015

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

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 ∆9-THC

- ∆9-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

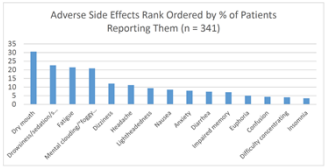
Individual AEs	No. of Studies (No. of Patients)	Summary OR (95% CI)
Dizziness	41 (4243)	5.09 (4.10-6.32)
Dry mouth	36 (4181)	3.50 (2.58-4.75)
Nausea	30 (3579)	2.08 (1.63-2.65)
Fatigue	20 (2717)	2.00 (1.54-2.62)
Somnolence	26 (3168)	2.83 (2.05-3.91)
Euphoria	27 (2420)	4.08 (2.18-7.64)
Depression	15 (2353)	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 for Pain

Iowa Qualifying Conditions:

Untreatable pain

Cancer – With **severe or chronic pain**

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**

Whiting et al., 2015 (Systematic Review)

- Whiting et al conclude :hat "…**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

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 (Nikseyet 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 chronic pain
  - In particular, neuropathic 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

Benefits for Multiple Sclerosis

Iowa Qualifying Condition:

Multiple Sclerosis with severe and persistent muscle spasms

Sativex (Nabiximols)

- 1:1 ratio of plant-derived THC:CBD
- Currently available in 30 countries outside the US for the treatment of multiple sclerosis and pain (UK, European Union, Canada, Israel)
- Currently in phase 3 trials in the United States and GW Pharma will be engaging with FDA to move forward with the drug approval process
- Standard marketing authorization: Sativex is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with MS who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy (Sativex Monograph, 2015)

Sativex (Nabiximols) (Continued)

- Standard marketing authorization ***with conditions***: Sativex may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with MS (Sativex Monograph, 2015)
- Standard marketing authorization **with conditions**: Sativex may be useful as adjunctive analgesic treatment in adult patients with advanced cancer pain who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (Sativex Monograph, 2015)
- Marketing authorizations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

American Academy of Neurology (Systematic Review, 2014)

Note that oral cannabis extract (OCE) contains BOTH THC and CBD

Do cannabinoids relieve spasticity in patients with multiple sclerosis (MS)?	
Strong evidence	Oral cannabis extract (OCE) is established as effective for reducing patient-reported scores (2 Class I studies)
Moderate evidence	OCE is probably ineffective for reducing objective measures at 12 to 15 weeks (1 Class I study)
	THC is probably effective for reducing patient-reported scores (1 Class I study)
	THC is probably ineffective for reducing objective measures at 15 weeks (1 Class I study)
	Sativex (nabiximols) is probably effective for reducing patient-reported symptoms at 6 weeks (1 Class I study) and probably ineffective for reducing objective measures at 6 weeks (1 Class I study)
Weak evidence	OCE is possibly effective for reducing objective measures at 1 year (1 Class II study)
	THC is possibly effective for reducing objective measures at 1 year (1 Class II study).
Insufficient evidence	Smoked marijuana is of uncertain efficacy (insufficient evidence)

Info from Koppel et al 2014 and associated Clinician Summary

American Academy of Neurology (Systematic Review, 2014)

Note that nabiximols (Sativex) is a 1:1 ratio of THC:CBD

What is the efficacy of using cannabinoids to treat central pain or painful spasms in MS?	
Strong evidence	**For patients with MS with central pain or painful spasms, OCE is effective for reduction of central pain** (2 Class I studies)
Moderate evidence	**THC or Sativex (nabiximols) (1 Class I study each) is probably effective for treating MS-related pain or painful spasms**
Insufficient evidence	Smoked marijuana is of unclear efficacy for reducing pain (2 Class III studies that examined different issues)

Do cannabinoids help treat bladder dysfunction in MS?	
Moderate evidence	Sativex (nabiximols) is probably effective for reducing the number of bladder voids per week at 10 weeks (1 Class I study)
	THC and OCE are probably ineffective for reducing bladder complaints (1 Class I study)
Insufficient evidence	Sativex (nabiximols) is of unknown efficacy in reducing overall bladder symptoms (contradictory Class I studies)

Info from Koppel et al 2014 and associated Clinician Summary

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 … spasticity due to MS.**"
  - Majority of studies evaluated for spasticity used Sativex (nabiximols) or a combination of THC/CBD

National Academies Report, 2017 (Systematic Review)

- **"There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity."** (National Academies Press Report, 2017)
  - "The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale." (National Academies Press Report, 2017)

Spasticity Due to Spinal Cord Injury

- National Academies Press
  - "Given the lack of published papers reporting the results of trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population." (National Academies Press Report, 2017)
- One problem is that studies of spasticity tend to lump spasticity due to MS and spasticity due to spinal cord injury together
  - Need additional studies examining the population with spinal cord injury to draw conclusions
- However, there is evidence that cannabinoids show efficacy in treating central neuropathic pain

Iowa Law

Qualifying Conditions in Iowa

- **Cancer – With severe or chronic pain**, nausea or severe vomiting, cachexia or severe wasting
- Seizures
- Crohn's disease
- *Ulcerative colitis likely to be added soon*
- **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
  - Best evidence for neuropathic pain
  - Particularly THC in combination with CBD
  - Some patients report a reduction in their other pain medications, including opioids
- Cannabinoids show efficacy in treating spasticity, pain, and painful spasms associated with MS in some patients
  - Evidence for efficacy in treating spasticity due to spinal cord injury is less robust
- 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)

Resources for Developing Practice Policies

Necessary Items

- Patient informed consent and treatment agreement
  - Additional information on following slides
- Form from Iowa Department of Public Health website
- Treatment algorithm for the practice
  - Plan in place to evaluate on case-by-case basis, if needed
- Guidelines for establishing relationship with the patient and determining what information to record in the medical record
- Input from attorneys experienced in healthcare law and who are familiar with the Iowa Medical Cannabidiol Act

Sample Patient Treatment Agreements

- Wilsey B et al, 2015:
  - **The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients Through a Written Document**
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4417655/
    - Sample agreement form included in the appendix; available for free
- University of Washington Cannabis Treatment Agreement
  - *adai.uw.edu/mcacp/docs/treatmentagreement.pdf*
- Can also leverage opioid agreements published by national pain medicine societies
  - American Academy of Pain Medicine - consent for chronic opioid therapy and consent for controlled substances are located here
    - http://www.painmed.org/library/clinical-resources/

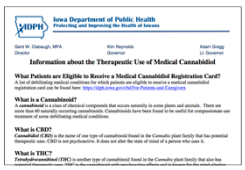
Form from IDPH Website

- https://idph.iowa.gov/cbd/For-Physicians

Patient Information Sheet for Health Care Practitioners

The Following document is an information sheet that physicians are required to discuss with patients. It provides explanatory information about the possible risks, benefits and side effects of medical cannabidiol.

- Patient Information Sheet



Iowa Department of Public Health
Protecting and Improving the Health of Iowans

Information about the Therapeutic Use of Medical Cannabidiol

What Patients are Eligible to Receive a Medical Cannabidiol Registration Card?

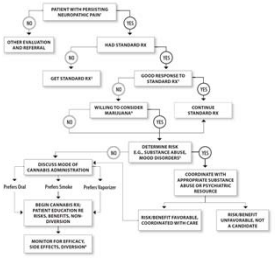
What is a Cannabinoid?

What is CBD?

What is THC?

Treatment Algorithm

- Helpful to create a decision tree or treatment algorithm that can handle most patients
- Sample in Grant et al., 2012
  - **Medical Marijuana: Clearing Away the Smoke**
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358713/



Guidelines for Physicians

- Federation of State Medical Boards:
  - https://www.fsmb.org/globalassets/advocacy/policies/model-guidelines-for-the-recommendation-of-marijuana-in-patient-care.pdf
- Oregon Medical Cannabis Guidelines for Physicians:
  - https://www.oregon.gov/oha/PH/PreventionWellness/marijuana/Documents/OHA-9262-Attending-Physician-Guidelines.pdf
- California Guidelines for Cannabis for Medical Purposes:
  - https://www.mbc.ca.gov/Publications/guidelines_cannabis_recommendation.pdf
- Iowa Department of Public Health – Medical Cannabidiol
  - https://idph.iowa.gov/cbd/For-Physicians

Case Study #2

- 53-year-old female
- Main pain complaint is low back pain and 3-4 occipital neuralgia headaches per week
- History of post-laminectomy syndrome and occipital neuralgia
- 14+ 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
    - Both 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

- 38-year-old male
- Injured elbow skiing, 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, patient uses it but has ongoing pain
- Patient employed, no longer on opioids, pain 7/10 daily

References

Abell TL, Kim CH, and Malagelada JR. Idiopathic cyclic nausea and vomiting – a disorder of gastrointestinal motility. Mayo Clin Proc. 1988;63(12):1169-75.

Abrams DI, Couey P, Shade SB, Kelly ME, and Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011 Dec;90(6):844-51.

American Academy of Pain Medicine (AAPM) Blog, 2016. Available at: http://blog.aapainmanage.org/. Accessed 01 June 2016.

American Academy of Pain Medicine (AAPM) Position Statement on National Decline in Opiod Prescribing. 23 April 2018. Available at: http://www.painmed.org/files/aapm-opioid-prescribing-decline-statement.pdf. Accessed 28 July 2018.

Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, Abrams DI, Prasad H, Wilsey B, Indyk D, Johnson M, and Sacks HS. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. J Pain. 2015 Dec;16(12):1221-1232.

Balabonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, and Walsh SL. Oral cannabidiol does not produce a safety signal for abuse liability in frequent marijuana smokers. Drug Alcohol Depend. 2017 Mar 1;172:9-13.

Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, Nunn A, Cano MG, MacManus D, Miller D, Mallik S, and Zajicek J. The cannabinoids use in progressive inflammatory brain disease (CUPID) trial: a randomized double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015;19(12):vii-viii, xxv-xxxi, 1-187.

Bradford AC, Bradford WD, Abraham A, and Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. JAMA Intern Med. 2018 May 1;178(5):667-672.

DEA, 2018. Available at: https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf. Accessed 27 July 2018.

Epidiolex Label, updated 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf_Accessed 22 July 2018.

Etges T, Karolia K, Grint T, Taylor A, Lauder H, Daka B, and Wright S. An observational postmarketing safety registry of patients in the UK, Germany, and Switzerland who have been prescribed Sativex (THC:CBD, nabiximols) oromucosal spray. Ther Clin Risk Manag. 2016 Nov 11;12:1667-1675.

GW Pharma, 2018. Available at: https://www.gwpharm.com/healthcare-professionals/sativex%C2%AE-delta-9-tetrahydrocannibinol-and-cannabidiol-eu-nabiximols-usa. Accessed 20 July 2018.

Hanus LO, Meyer SM, Munoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Nat Prod Rep. 2016 Nov 23;33(12):1357-1392.

Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. JAMA. 2015 Jun 23-30;313(24):2474-83. Erratum in: JAMA. 2016 Sep 6;316(9):995.

Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and pain: A clinical review. Cannabis Cannabinoid Res. 2017;2(1):96-104.

Hunault CC, Bocker KB, Stellato RK, Kenemans JL, de Vries I, and Meulenbelt J. Acute subjective effects after smoking joints containing up to 69 mg delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. Psychopharmacology (Berl). 2014 Dec;231(24):4723-33.

Iowa House File 524. Available at: https://www.legis.iowa.gov/legislation/BillBook?ga=87&ba=hf524. Accessed 28 June 2018.

Iowa Department of Public Health, 2018. Available at: https://idph.iowa.gov/cbd/For-Patients--and-Caregivers. Accessed 27 August 2018.

Karschner EL, Darwin WD, Goodwin RS, Wright S, and Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta-9 tetrahydrocannabinol and oromucosal cannabis extract administration. Clin Chem. 2011;57(1):66-75.

References (Continued)

King LA. Legal controls on cannabimimetics: an international dilemma? Drug Test Anal. 2014 Jan-Feb;6(1-2):80-7.

Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, and Gloss D. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders. Neurology 2014;82:1556-1563. Clinician summary available at:

Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, and Blanco C. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2011 May 1;115(1-2):120-30.

Mackie K and Stella N. Cannabinoid receptors and endocannabinoids: evidence for new players. AAPS J. 2006 Apr 28;8(2):E298-306.

Marinol Label, updated 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf. Accessed 27 July 2018.

Mark Wallace, 2018. Phone interview conducted with Mark Wallace, MD on 31 July 2018.

Mark Ware, 2018. Phone interview with Mark Ware, MD, conducted on 19 July 2018.

Melville, Nancy. 2018. Medical Cannabis for Pain May Reduce Need for Opioids. Available at: . Accessed 20 August 2018.

Minnesota Department of Health, Office of Medical Cannabis. Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months. St. Paul, MN 55164-0882. Available at: http://www.health.state.mn.us/topics/cannabis/about1preport.pdf

Morales P, Hurst DP, and Reggio PH. Molecular targets of the phytocannabinoids: A complex picture. Prog Chem Org Nat Prod. 2017;103:103-131.

Minnesota Statute 152.125. Available at: https://www.revisor.mn.gov/statutes/cite/152.125. Accessed 28 July 2018.

Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Candaian Pain Society. Pain Res Manag. 2014;19(6):328-35.

Nabilone Label, updated 2006. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf_Accessed 21 July 2018.

National Academies Press. The health effect of cannabis and cannabinoids: The current state of evidence and recommendations for research. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The National Academies Collection: Reports Funded by the National Institutes of Health. 2017.

NIDA, 2017. Available at: https://www.drugabuse.gov/about-nida/noras-blog/2017/04/addressing-americas-fentanyl-crisis

NIDA, 2018a. Available at: https://www.drugabuse.gov/publications/drugfacts/synthetic-cannabinoids-k2spice

NIDA, 2018b. Available at:

References (Continued)

Ridenhour TA, Lanza ST, Donny EC, and Clark DB. Different lengths of times for progressions in adolescent substance involvement. Addict Behav. 2006;31(6):962-983.

Sativex Mongraph, updated 2015. Available at: https://omr.bayer.ca/omr/online/sativex-pm-en.pdf. Accessed 28 July 2018.

Savage SR, Romero-Sandoval A, Schatman M, Wallace M, Fanciullo G, McCarberg B, and Ware M. Cannabis in pain treatment: Clinical and research considerations. J Pain. 2016 Jun;17(6):654-68.

Syndros Label, updated 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205525s000lbl.pdf_Accessed 23 July 2018.

Wallace MS, Marcotte TD, Umlauf A, Gouaux B, and Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015 Jul;16(7):616-27.

Ware MA, Wang T, Shapiro S, Collet JP, and COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015 Dec;16(12):1233-1242.

Wen H and Hockenberry JM. Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. JAMA Intern Med. 2018;178(5):673-679.

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, and Kleijnen J. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.

Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, and Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136-48.

Wilsey B, Atkinson JH, Marcotte TD, and Grant I. The medicinal cannabis treatment agreement: Providing information to chronic pain patients via a written document. Clin J Pain. 2015;31(12):1087-1097.

Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, and Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain. 2016 Sep;17(9):982-1000.

WHO, 2018. Fortieth meeting of the Expert Committee on Drug Dependence. Pre-reviews on cannabis plant and resin, extracts and tinctures of cannabis, delta-9-tetrahydrocannabinol (THC), and isomers of THC. Available at: http://www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/.

WHO CBD Report, 2018. Fortieth meeting of the Expert Committee on Drug Dependence. Critical Review: Cannabidiol. Available at: http://www.who.int/medicines/access/controlled-substances/WHOCBDReportMay2018-2.pdf. Accessed 15 July 2018.

Zou S and Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. Int J Mol Sci. 2018 Mar 13;19(3).