# **Clearing the Smoke**

**The Final Update?** 

Jeremy Daniel, PharmD, BCPS, BCPP Associate Professor, SDSU College of Pharmacy and Allied Health Professions Clinical Pharmacist, Avera Behavioral Health Center September 9, 2022

### Disclosure

 This speaker has no conflicts of interest or commercial financial relationships with the information presented today

# **Pharmacist Learning Objectives**

- Describe the pharmacogenomics impact of cannabinoid use
- Compare and contrast the different THC compounds available recreationally
- Evaluate the relationship between marijuana use and the opioid epidemic

# **Technician Learning Objectives**

- Define who has certification authority for medical cannabis
- Describe the differences in effects of various cannabinoids
- List clinical effects of recreational marijuana use

# Why Are We Talking About This?

- Almost a year since state started issuing cards
- First dispensaries are popping up
  - The Flower Shop Dispensary in Sioux Falls opened 09/02/2022
- South Dakota marijuana crop coming soon
   Smaller batches already here
- Recreational marijuana IM vote on the horizon

# Who Can Certify for Medical Cannabis?

- Previously only physicians
- Now
  - Physicians
  - Physician Assistants
  - Advanced Practice Registered Nurses
- Currently no list of certified providers

### **How Many Providers Can Certify?**

# Minimal movement here Patient numbers increasing, however

WEEKLY PRACTITIONER AND PATIENT CARD NUMBERS

August 29, 2022

150 APPROVED PRACTITIONERS

2,484 APPROVED PATIENT CARDS WEEKLY PRACTITIONER AND PATIENT CARD NUMBERS

August 22, 2022

150 APPROVED PRACTITIONERS

2,277 APPROVED PATIENT CARDS WEEKLY PRACTITIONER AND PATIENT CARD NUMBERS

August 17, 2022

149 APPROVED PRACTITIONERS

2,177 APPROVED PATIENT CARDS

Note, this does not include cards from reservations

Medcannabis.sd.gov

### Didn't We Already Talk About Medical Benefits?

### Yes!

- Nausea/vomiting Low
- Appetite stimulation Low/moderate
- Glaucoma Low
- Epilepsy CBD = High, whole plant = low/moderate
- Pain management High
- PTSD Short term/PRN = High, long term/chronic = low/may cause harm
- Crohn's Disease Moderate
- Multiple Sclerosis Pain/spasms/spasticity = High, everything else = Low
- So, we're not going to again today

# What Are We Covering Today?

- Drug Interactions
- The "different deltas" of THC
- Impairment and testing
- Recreational marijuana Impacts

### Are There A Lot of Drug Interactions?

- THC inhibits CYP:
  - 1A2, 1B1, 2B6, 2C9, 2C19, 2D6, 2J2
  - Medications like clozapine (1A2), methadone (2B6,2C19), warfarin (2C9), and most beta blockers (2D6)
- CBD inhibits CYP:
  - 1A2, 1B1, 2C9, 3A4/5/7 (potentially)
  - Numerous antiepileptics and DOACs (3A4)
- Smoking induces CYP 1A2
  - Burned hydrocarbon is the inducer
  - Induction normally wins with smoking
  - This does not apply to vaping (unless high heat), edibles, or dabs (concentration too high)
- Degree of inhibition depends on potency
  - Low potency likely to have minimal effect

### Does Marijuana Impact Anticoagulants

#### Warfarin

- Limited to case reports of elevated INR
- 2020 review article recommends close INR monitoring with changes in cannabis intake

#### DOACs

- Limited to theoretical interactions only
- No case reports published
- Monitoring?
- P2Y12 Inhibitors
  - CYP2C19 inhibition may affect clopidogrel conversion
  - 2013 Jiang article argues interaction is significant
- Schedule I status and ethics may limit study

Brown GW et al. J Am Parrm Assoc. 2021 Damiker P et al. Basic Clin Pharmacol Toxicol. 2019 Hsu A et al. J Pharm Pract. 2020 Paduch M et al. Hosp Pharm. 2022 Greger J et al. J Clin Pharmacol. 2020 Jiang R et al. Drug Metab Pharmacokinet. 2013

### What About Induction of 1A2?

### Older theophylline studies

- Jusko studies (n=257)
  - Smoking marijuana while taking theophylline
  - At least 2 joints/week (dose?) increase clearance by 42-48%
    - 1 joint per week increased clearance by 4%
  - When combined with tobacco, clearance increase 79%
- Gardner study (n=49)
  - Infrequent use yielded no change
- Chlorpromazine also affected
  - 1994 study showed 50% increase in clearance
    - IO7% increase when combined with tobacco

Stout SM et al. Drug Metab Rev. 2014 Jusko WJ et al. J Pharm Sci. 1979 Jusko WJ et al. Clin Pharmacol Ther. 1978 Gardner MJ et al. Br J Clin Pharmacol. 1983 Chetty M et al. Eur J Clin Pharmacol. 1994

### What Are The Different Deltas?

- Delta-9 THC is from marijuana plant
- Delta-8 and delta-10 THC are synthetically derived from hemp
  - 2018 Farm Bill allows products to be derived from hemp
    - Must be for industrial purpose, not human consumption
- In smoke shops, delta-8 and delta-10 are in vapes
  - Most commonly with CBD

### What is Delta-8 THC?

- Structurally similar with moved double bond
- Binding affinity for CB1 and CB2 receptors lower than delta-9 THC
  - Ki about 6x higher for delta-8
- Reported to produce more "mellow" high
- FDA and poison control centers receiving many reports



### How Bad Are These Reports?

- FDA received 104 adverse event reports
  - 12/01/2022 02/28/2022
  - 77% adults, 8% peds
  - 55% required intervention or hospital admission
  - 66% linked to food products remember why? (next slide)
  - Hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and LOC
- Poison control centers received 2,362 exposures
  - 01/01/2021 02/28/2022
  - 58% adults, 41% peds
  - 40% were unintentional, 82% of those in peds
  - 70% required hospital evaluation/admission
    - 8% ICU admit
  - One pediatric death
- If lower affinity, why the issue?
  - All about dosing

# Why Are Edibles Higher Risk?

- Smoking/vaping
  - Most common method
  - Onset of high = seconds/minutes
  - Peak effects ~ 30 minutes
  - "Come down" ~ 1-3 hours
  - Specific effects depend on temperature or vape

### Dabbing

- Flash vaporization of hash oils
- Similar pharmacokinetics of smoking/vaping above
- Increased effects due to elevated THC content of oils

### Edibles

- All kinetics delayed
- Onset of high = 30-120 minutes
- Peak effects ~ 2-4 hours
- "Come down" ~ 5-8 hours
- Significant bioavailability differences (20-40%)
- Topical products?
  - Does not enter bloodstream
  - May target CB receptors in skin
  - Most benefit appears to be from application

### What About Delta-10?

 Structurally similar with moved double bond



- Binding affinity not well studied
  - Appears lower
- Reported to produce more "energetic" high
- Limited toxicology data exists

### **Visual Representation**

### Comparing The Effects of THC Isomers

#### Relaxing

- Relaxing
- Sedating
- Muscle-Relaxant
- Increased Hunger

#### Stimulating

- Stimulating
- Euphoric
- Increased Hunger
- Creativity





Delta 8 THC





#### Delta 9 THC

#### Delta 10 THC Image from DailyCBD – not a medical source

### Remind Me Of THC vs. CBD again?

- THC (tetrahydrocannabinol)
  - Most common molecule in cannabis
  - Responsible for psychoactive effects
  - Triggers release of dopamine
- CBD (cannabidiol)
  - Second most common molecule in cannabis
  - Down-regulates effects of THC
  - Medical benefit
- CBC (cannabichromene)
  - Third most common molecule in cannabis
  - Non-intoxicating
  - Potential antineoplastic benefit?
    - 2013 mouse study by Nakajima et al. in Journal of Pharmacy and Pharmacology



### What About Impairment?

- We've previously discussed the Akrell 2020 article
  - 26 participants between 20-50 with driving experience
  - Used THC, CBD, 50/50 mix, and placebo (dose = 13.75 mg)
  - Drove 100 km at 40 minutes and 240 minutes after use
  - Measured "standard deviation of lateral position"
  - Results SDLP between 40-100 minutes after use
    - CBD = 18.21 cm
    - THC = 20.59 cm
    - Mix = 21.09 cm
    - Placebo = 18.28 cm
  - + 2.31 cm in THC group compared to placebo (stat sig)
  - No difference at 240 minute mark
  - Only 16 drives terminated due to safety concerns (most 240 minute drives)
- For comparison, BAC of 0.05% yields 2.4cm SDLP

### **Other Impairment Articles?**

- 2022 article from JAMA Psychiatry
  - 191 cannabis users randomized to 3 groups
  - Experienced users averaged 16.7 days of use in past month
  - Placebo, 5.9% THC, or 13.4% THC smoked "ad libitum"
  - Tested on Composite Driving Score
  - Results
    - Significant decline on CDS at 30 and 90 minutes
    - Borderline differences at 210 minutes, no difference at 270 min
    - THC content did not affect score
    - <u>Post-smoking THC blood concentrations dud not predict</u> <u>impairment</u>
    - Users were more willing to drive at 90 minutes

### So, How Do We Test For Impairment?

- 2021 article in Traffic Injury Prevention by Arkell
  - 14 infrequent users of marijuana (eliminates tolerance)
  - Exposed to 125 mg of THC, THC/CBD mix, or placebo
  - Tested pre-determined cutoffs from previous studies
    - 1.4 and 7 ng/mL in plasma (correlates to 1 and 5 ng/mL in whole blood)
    - 2 and 5 ng/mL in oral fluid
  - Drove at 30 minutes and 3.5 hours
  - Failure defined as > 2cm SDLP compared to placebo
  - Results
    - All non-placebo participants over the limit at 30 minutes
    - Only 46% of users failed to meet SDLP criteria
    - At 3.5 hours, 57% showed impairment despite low levels
  - Key take-aways
    - Impairment can be present with low levels
    - Positive THC doesn't always mean impairment

### What Else Influences Marijuana Impairment?

### Non-modifiable

- Genetics and metabolism
- Personal/family mental health history
- Comorbidities
- Modifiable
  - Route
  - Dose
  - Composition of marijuana
  - Drug interactions
  - Tolerance
  - Other substances used

### What Else Can We Do?

- Try to mitigate risk
  - Stabilize dose for 2 weeks prior to engaging in driving
  - Regulated suppliers
  - Keep doses low (< 10 mg/day is possible)</p>
  - Wait 4-6 hours after inhaling or 6-8 hours after oral ingestion
  - Limit sedatives and interacting meds
  - Monitor and educate patient

### What About Recreational Use?

- Amendment A passed, then removed in court
- IM 27 is coming this fall
  - Legalizes possession, use, distribution (including paraphernalia) by 21+ individuals
  - Limited to 1 ounce
  - May grow plants under "specific conditions"
    - Only in "counties or cities where no licensed retail marijuana store is available"

### Will This Impact The Opioid Issue?

- Short answer maybe?
- Commonly cited 2014 pro-legalization article
  - Compared opioid overdose deaths in states with/without medical marijuana from 1999-2010
  - Results
    - States with medical laws had 24.8% lower opioid overdose mortality
    - Rate of mortality decreased over time after legalization
    - Overdose rate was stable prior to passage
  - Limitation many confounders exist

### What About Newer Literature?

- Newer literature tells a different story
- 2019 PNAS article
  - Similar structure as previous study
  - Included years 2010-2017
  - After 2012, no difference between legalized states and non-legalized states
  - In 2017, medical marijuana was positively correlated
- 2021 Pharmacopsychiatry article
  - Reviewed full range 1999-2017
  - Medical cannabis positive correlated to overdoses after 2017
  - Confounded by lower overdose reporting in non-medical states (2) compared to medical states (11)
- Also need to consider the Triple Wave' role

### What's the Triple Wave?



SOURCE: National Vital Statistics System Mortality File.

### Are Use Rates Decreasing?

### Short answer – not really

Maybe in school-aged kids when separated out

Figure 9. Past Year Illicit Drug Use: Among People Aged 12 or Older; 2020



### Are Use Rates Decreasing?

Figure 11. Past Year Marijuana Use: Among People Aged 12 or Older; 2002-2020



### **Clinical Pearls**

- Numerous drug interactions exist
  - Clinical validity still pending for most
  - Monitor narrow-therapeutic index medications more closely
- Different deltas produce different effects
  - Delta-8 tends to be more calming and predictable
  - Delta-10 is more energizing
  - Both still cause issues
- Impairment is challenging to measure
  - Levels do not correlate well
  - Impairment influenced by many factors
- May or may not help opioid epidemic
  - Data is mixed
  - Influenced by may confounders

### Pharmacist Question 1

- Which of the following medications would undergo induction with smoked marijuana use?
  - A. Metoprolol (CYP2D6)
  - B. Warfarin (CYP2C9)
  - C. Theophylline (CYP1A2)
  - D. Clopidogrel (CYP2C19)

### **Pharmacist Question 2**

- Which of the following is TRUE when comparing delta-8 THC to delta-10 THC?
  - A. Delta-8 produces more of an energizing effect
  - B. Delta-8 has more consistent reports of adverse events
  - C. Delta-8 binds more strongly to CB1 receptors
  - D. Delta-8 is illegal while delta-10 is legal

### **Pharmacist Question 3**

- Per the studies presented, which of the following most closely describes the relationship between opioid overdoses and marijuana legalization?
  - A. Prior to widespread use of non-prescription opioids, marijuana legalization showed a decrease in opioid overdoses
  - B. After widespread use of non-prescription opioids, marijuana legalization showed a decrease in opioid overdoses
  - C. Increased use of non-prescription opioids further strengthened marijuana's overdose reduction
  - D. All of the above

### Technician Question 1

- After the July law update, which of the following providers has certification authority for medical cannabis in South Dakota?
  - A. Physicians
  - B. Physician Assistants
  - C. Advanced Practice Registered Nurses
  - D. All of the above

### **Technician Question 2**

- Which of the following is TRUE when comparing delta-8 THC to delta-9 THC?
  - A. Delta-8 binds more strongly to the CB1 receptor
  - B. Delta-8 requires lower doses to have the same effect
  - C. Delta-8 is more "calming" than delta-9
  - D. Delta-8 is safer than delta-9

# **Technician Question 3**

- Which of the following is TRUE regarding effects on driving results from marijuana use?
  - A. Blood levels are a positive predictor of impairment
  - B. Oral fluid levels are a positive predictor of impairment
  - C. Low doses of marijuana demonstrate similar SDLP to legal limit of alcohol (BAC = 0.08%)
  - D. Significant impairment can be present without "per se" limit

### **Questions?**

Jeremy Daniel, PharmD, BCPS, BCPP Associate Professor, SDSU College of Pharmacy and Allied Health Professions Clinical Pharmacist, Avera Behavioral Health Center September 9, 2022