Medical Cannabis
Delving into the Weeds

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Disclosures

• None
Agenda

- History of how cannabis came to be illegal
- Current laws, regulations, and research challenges
- Cannabis and cannabinoids
- Use of cannabis and its effects
- Data for therapeutic effects and adverse effects
- FDA-approved medications
- Cannabis and renal disease
- Cannabis and the opioid epidemic
- Bottom line, practical approach to medical cannabis
What Do We Mean by Cannabis?

• Cannabis:
  – A psychoactive drug from the Cannabis plant used for medical or recreational purposes

• Don’t you mean marijuana?

Wang 2019, Wikipedia 2019
History and Laws
Early Days

NASEM 2017, Wikipedia 2019
So What Went Wrong?

• 1906 – Pure Food and Drug Act passed
• 1910s – Mexican Revolution
• 1930 – Federal Bureau of Narcotics formed
Harry Anslinger

- “Marijuana is the most violence-causing drug in the history of mankind…and most [marijuana smokers] are Negroes, Hispanics, Filipinos, and entertainers. Their satanic music, jazz, and swing, result from marijuana usage. This marijuana causes white women to seek sexual relations with Negroes, entertainers, and any others.”
- “Reefer makes darkies think they’re as good as white men…the primary reason to outlaw marijuana is its effect on the degenerate races.”

Wikipedia 2019, Wilcox 2014
More Laws

• 1937 – Marihuana Tax Act

• 1970 – Controlled Substances Act

Wikipedia 2019, Wilcox 2014
The Times They Are A Changin’

- 1996 – CA Proposition 215 approved
- 2012 – CO and WA legalized recreational use

NC:
- 1977 – Decriminalized
- 2015 – CBD legalized for intractable epilepsy
- 2017 – Hemp farming legalized

Wikipedia 2019
Public Opinion and Use

Majorities of All Political Identification Groups Continue to Support Legalization of Marijuana in 2018

% Yes, marijuana should be made legal

- Republicans
- Independents
- Democrats

GALLUP

Wang 2019, Wikipedia 2019
Research Difficulties
Cannabis
Cannabis

- **Sativa**
  - Very tall
  - Long branches with large distances between nodes
  - Expansive root system
  - Long, thin leaves

- **Indica**
  - Small, compact size
  - Condensed root system
  - Robust stalks
  - Wide leaves
  - Dense, heavy buds

- **Ruderalis**
  - Small in size and wild-looking
  - Fewer branches than Sativa or Indica specimens
  - Conical shape

Rahn 2018, Wikipedia 2019
Cannabinoids

The Human Endocannabinoid System

CB1 Receptors are mostly found in the Nervous System and Brain

CB2 Receptors are mostly found in the peripheral organs, especially immune cells

THC and CBD

Tetrahydrocannabinol (THC)

Cannabidiol (CBD)

Cannabinoid System

- Partial Agonist
  - CB1: Negative Allo Modulator
  - CB2: Weak Agonist

Serotonin Receptors

- No effect
  - 5-HT1A: Full agonist
- No effect
  - 5-HT2A: Weak Partial Agonist
- Negative Allo Modulator
  - 5-HT3A: Negative Allo Modulator

Dopamine Receptors

- Not Tested
  - D2High: Partial agonist

Opioid Receptors

- Negative Allo Modulator
  - uOR: Negative Allo Modulator
- Negative Allo Modulator
  - δOR: Negative Allo Modulator

Christensen 2018
NASEM 2017
Rahn 2018
Wikipedia 2019
Using Cannabis

• Routes

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>&lt;15 min</td>
<td>1 – 3.5 h</td>
</tr>
<tr>
<td>Oral</td>
<td>30 min – 3 h</td>
<td>5 – 8 h or longer</td>
</tr>
<tr>
<td>Topical</td>
<td>15 – 45 min</td>
<td>2 h</td>
</tr>
</tbody>
</table>

• Products

<table>
<thead>
<tr>
<th>Product</th>
<th>THC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flowers</td>
<td>5-20%</td>
</tr>
<tr>
<td>Resin</td>
<td>40-80%</td>
</tr>
<tr>
<td>Oil</td>
<td>75+%</td>
</tr>
</tbody>
</table>

What Happens When We Use?

• With Effective Doses:
  – Decreased short term memory
  – Impaired perception and motor skills
  – Ataxia
  – Slurred speech
  – Enhanced sensitivity to stimulation
  – Altered perception of time
  – Increased appetite
  – Euphoria
  – Red eyes
  – Decreased intraocular pressure
  – Dry mouth
  – Tachycardia
  – Orthostatic hypotension
  – Tachypnea
  – Muscle relaxation

• With Very High Doses:
  – Psychosis
  – Hallucinations
  – Paranoia
  – Panic attacks
  – Asthma exacerbations
  – Pneumomediastinum
  – Pneumothorax
  – Acute coronary syndrome
  – Cannabis hyperemesis syndrome

• What about overdose, withdrawal, or dependence?

Let’s Talk about Data

The Health Effects of Cannabis and Cannabinoids

CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

Aggarwal 2015, NASEM 2017
Therapeutic Effects

• Conclusive/Substantial Evidence for Effectiveness:
  – Chronic pain in adults
  – Chemotherapy-induced nausea/vomiting
  – Patient-reported multiple sclerosis-related spasticity

• Moderate Evidence for Effectiveness:
  – Sleep disturbance related to OSA, fibromyalgia, chronic pain, MS

NASEM 2017
Therapeutic Effects

• Limited Evidence for Effectiveness:
  – HIV/AIDS-related anorexia and wasting
  – Clinician-reported MS-related spasticity
  – Tourette syndrome
  – Anxiety
  – PTSD
  – Better outcomes after TBI/ICH

• Limited Evidence for Ineffectiveness:
  – Dementia
  – Glaucoma
  – Depression in patients with chronic pain or MS
Therapeutic Effects

• No/Insufficient Evidence for Effectiveness:
  – Cancer
  – Cancer-related anorexia
  – Irritable bowel syndrome
  – Epilepsy
  – Spasticity in patients with spinal cord injury
  – ALS
  – Huntington’s disease
  – Parkinson’s disease
  – Dystonia
  – Abstinence from other addictive substances
  – Schizophrenia

NASEM 2017
Effects for Movement Disorder

MAN WITH SEVERE PARKINSON'S DISEASE

TRIES MARIJUANA FOR THE FIRST TIME

YouTube 2017
Adverse Effects

• Substantial Evidence:
  – Worse respiratory symptoms with bronchitis (smoking)
  – Increased risk of motor vehicle crashes
  – Lower birthweight of infants
  – Development of schizophrenia

• Moderate Evidence:
  – No increased risk of lung or head/neck cancer (smoking)
  – Increased risk of overdose injuries in children in legal states
  – Increased risk of depression, mania in bipolar disorder, social anxiety disorder, suicidal ideation and completion
  – Development of substance use disorder of other substances

NASEM 2017
Therapeutic Effects

- Limited Evidence:
  - Increased incidence of some testicular cancers (smoking)
  - Triggering acute MI (smoking)
  - Increased risk of stroke
  - Decreased risk of diabetes and metabolic syndrome
  - Increased risk of developing COPD
  - Pregnancy complications for mother
  - NICU admissions for infants
  - Impaired academic, employment, or social achievement
  - Increase in positive symptoms for those with psychosis
  - Increased risk of developing bipolar disorder or anxiety
  - Increased severity of PTSD
  - Initiation of tobacco abuse

NASEM 2017
Therapeutic Effects

• No/Insufficient Evidence:
  – Incidence of other cancers
  – Developing asthma
  – COPD hospitalizations
  – Adverse immune responses
  – All-cause mortality
  – Occupational accidents
  – Later infant outcomes (i.e.. Not right after birth)
  – Developing PTSD
FDA-Approved Medications

- Dronabinol (Marinol)
- Nabilone (Cesamet)
- Epidiolex

Davison 2011, NASEM 2017
Dronabinol (Marinol)

- Synthetic delta-9-THC
- Approved for chemo-induced nausea/vomiting and AIDS-related anorexia
- Formulation: Oral capsule and solution
- No adjustment for renal or hepatic dysfunction
- No lab monitoring
- Onset: 30-60 minutes
- Duration: 4-6 hours
- Half life: 19-56 hours
- Urine THC positivity: Yes

Davison 2011, NASEM 2017
Nabilone (Cesamet)

- Synthetic analog of delta-9-THC
- Approved for chemo-induced nausea/vomiting
- Formulation: Oral capsule
- No adjustment for renal or hepatic dysfunction
- No lab monitoring
- Onset: 60-90 minutes
- Duration: 8-12 hours
- Half life: 2 hours
- Urine THC positivity: No

Davison 2011, NASEM 2017
Epidiolex

- Concentrated (98%) CBD oil
- Approved for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients >2 yo
- Formulation: Oral solution
- No adjustment for renal dysfunction
- Adjustment needed for hepatic dysfunction
- Monitor LFTs due to risk of hepatotoxicity
- Onset: Within 4 weeks
- Half life: 56-61 hours
- Urine THC positivity: No

Davison 2011, NASEM 2017
Nabiximols (Sativex)

- THC:CBD extract from 2 Cannabis varieties
- Not approved in US
- Approved in other countries for MS-related spasticity or neuropathic pain
- Formulation: Buccal/oral spray
- No adjustment for renal or hepatic dysfunction
- No lab monitoring
- Onset: 30-150 minutes
- Duration: 6-8 hours
- Half life: 1.5 hours
- Urine THC positivity: Yes

Davison 2011, NASEM 2017
Cannabis and Renal Disease

- THC partially excreted in urine
  - Effects *may* last longer
- CBD mostly excreted in feces
  - Effects *may* not be effected
- Cannabinoids highly protein bound and lipid soluble
  - *May* not be dialyzed well
- Renal system has CB1 and CB2
  - No data on effects

Aggarwal 2015, Davison 2011, Ho 2019, NASEM 2017
Symptom Relief for CKD?

Is There a Legitimate Role for the Therapeutic Use of Cannabinoids for Symptom Management in Chronic Kidney Disease?

Sara N. Davison, MD, and Joseph S. Davison, PhD
Division of Nephrology and Immunology (S.N.D.), University of Alberta, Edmonton; and Department of Physiology and Biophysics (J.S.D.), University of Calgary, Calgary, Alberta, Canada

Davison 2011, Ho 2019
Renal-Specific Data

- Cohort of 21 patients undergoing HD with uremic pruritus
- Cream with lipids and cannabinoids bid for 3 weeks
- Pruritus completely eliminated in 38%
- Xerosis completely reduced in 81%
- Xerosis intensity did not correlate with pruritus severity
  - Assumed that xerosis was not the main contributor to pruritus
- No adverse effects
Renal-Specific Data

Cohort study of 7 patients s/p kidney transplant with chronic pain who asked to receive CBD to treat their pain
- CBD 50mg bid increased up to 150mg bid for 3 weeks
- 2 had total pain improvement, 4 had partial, 1 had no change
- Adverse effects: nausea, dry mouth, dizziness, drowsiness
- CBD dose reduction was needed in 2 patients
- Tacrolimus levels may have been effected


Chronic Pain Treatment With Cannabidiol in Kidney Transplant Patients in Uruguay.
Cuñetti L, Manzo L, Peyraube R, Arnaiz J, Curi L, Orihuela S.

Cuñetti 2018
Cannabis and the Opioid Epidemic
Cannabis and the Opioid Epidemic

Fewer deaths does not mean cause and effect
Laws don’t address non-prescription opioid abuse
Only case reports about using cannabis to taper
No evidence for use to treat opioid use disorder
Strong evidence-based treatments are underutilized
Cannabis and the Opioid Epidemic

• Highlighted largest cohort study with cannabis as a substitute
  – 1500 patients over 4 years
  – Associated with more pain, less self-efficacy, and same opioid use
• Using cannabis to treat opioid use disorder is using the failed tactic of replacing addictive substances with others
• Cannabis products are highly variable
  – Of 84 studied CBD extracts, 69% were mislabeled
• Risks have evidence, substitution does not
What’s the Bottom Line?

“Yeah, well, you know, that’s just like, your opinion, man.

Jeffrey ‘The Dude’ Lebowski
Overall Approach

• Practical approach from American Pain Society:
  – Know federal and state laws governing medical cannabis
  – Be clear with patients about goals for therapeutic cannabis
  – Screen for risk of misuse, addiction, and diversion
  – Counsel patients about routes, benefits, risks
  – Advise patients on strains, medications, extracts, limitations
  – Monitor patients as you would for treatment with opioids
  – Assess progress toward achieving goals, side effects
  – Continue or discontinue based on observed outcomes

Savage 2016, VandeKieft 2018
Approach for Chronic Pain

- Think about cannabis before opioids
- Should be part of an integrated, patient-centered program emphasizing non-pharmacologic options
- Oral capsules for long action, tinctures/vaping for short action
- Start low (with CBD) and go slow:
  - CBD 5-10mg PO bid
  - Increase weekly over 1-2 months until relief
  - If no relief, add THC 1-2mg and slowly increase
- Delayed THC hopefully avoids dysregulation of endocannabinoid system (extrapolated from opioid use)

Boehnke 2019
My Takeaways

• The history of how cannabis became illegal is concerning
• Research needs to be easier than it is
• Start with low THC, go slow
• Vaporize for short-term, oral for long-term, don’t smoke
• Not a magic bullet, but another tool in the toolbox for challenging symptoms
• Use definitely has real risks
• Sounds safe in patients with renal dysfunction
• Definitely not the solution to the opioid epidemic
References

References


References


References


Questions and Thank You!

THANK YOU, CANNABIS.

- For helping me to get to bed.
- For giving me the motivation to write.
- For introducing me to great friends.
- For keeping me sane when my life fell apart.
- For introducing me to the love of my life.
- For accepting me and helping me accept myself.
- For making my joints and back feel better.
- For fixing my insomnia.
- For helping me deal with my stomach ulcer pain.
- For helping me with my anger issues.
- For helping me with my bi-polar disorder.
- For getting rid of my anorexia.
- For helping me keep a positive outlook.
- For treating my depression and anxiety.
- For fixing my chronic headaches.
- For fending off my panic attacks.
- For making my IBS bearable.
- For opening my mind to art and imagination.
- For being there for me when no one else was.