Impact of Marijuana Use on Patient Care: From Recreation to Reconciliation

CPFI 2018 Conference
Bonclarken Conference Center
Flat Rock, North Carolina

Cathy Rosenbaum PharmD MBA RPh CHC
Founder & CEO, Rx Integrative Solutions
Loveland OHIO

Copyright 2018

Disclaimer

- I have no financial interest or direct affiliation with any company or organization involved with medical or recreational marijuana or hemp products.
- This is an educational program. Please consult with your PCP for medical advice.

Objectives

- Discuss legal landscape and product quality-related issues regarding recreational marijuana
- Review significant marijuana side effects and common drug interactions
- Describe ‘at risk’ patient populations using recreational marijuana case scenarios
- Review the pharmacist-led hospital admission MedRec process & marijuana policy development for health systems

International MJ Legislation

<table>
<thead>
<tr>
<th>Country</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Canada</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>India</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Jamaica</td>
<td>Spain</td>
</tr>
<tr>
<td>Mexico</td>
<td>Uruguay</td>
</tr>
</tbody>
</table>

29 Legal Medical Marijuana States & DC
9 Legal Recreational Marijuana States & DC

[Map showing legal status of marijuana use]
States/Territories Permitting Recreational Marijuana Use

- Colorado (2012)
- Washington (2012)
- Alaska (2014)
- District of Columbia (2014)
- Oregon (2014)
- California (2016)
- Massachusetts (2017)
- Nevada (2017)
- Maine (2017)
- Vermont (2018)

Oregon Recreational Marijuana Retail Sale Limits

Introduction to Cannabis

- Cannabis (marijuana) is the most common and widely used illicit drug.
- A product's chemical profile is more important than the strain of plant from which it originated.
- Products should be characterized by analytical chemistry - percentages of cannabinoids and terpenoids.

Δ-9-THC Detection

- **Serum** – Active THC (cannabinoids) (positive at 20 ng/mL) MedTox Immunochromatographic test
- **Urine** – Inactive THC-COOH-glucuronide (positive at 50 ng/mL). Answers, “has this person used cannabis over the last days or weeks?”

Levels of THC or metabolites do not correlate with efficacy or toxicity.
Detected in the Urine

<table>
<thead>
<tr>
<th>THC-COOH-Glucuronide</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Use</td>
<td>3 Days</td>
</tr>
<tr>
<td>Moderate Use (4x/week)</td>
<td>5 – 7 Days</td>
</tr>
<tr>
<td>Daily Use</td>
<td>10 – 15 Days</td>
</tr>
<tr>
<td>Long-Term Heavy Smoker</td>
<td>&gt; 30 Days</td>
</tr>
<tr>
<td>THC - T 1/2</td>
<td>2 – 7 Days</td>
</tr>
</tbody>
</table>

Recreational Marijuana Issues

- Quality control/product safety (legal vs street)
- Lingering contaminants in marijuana sold on the street
- Dealers typically sell cannabis by weight; some use sand or glass beads to make their products heavier
- Breathing these particles over years may inflame and scar the lungs
- Higher THC content than medical marijuana limits?
- Not detectable with Breathalyzer test
- Risk of accidents for drivers with THC levels higher than 5 ng/mL blood (similar to blood alcohol concentration of 0.08%)

Dabbing

- Flash vaporizing butane hash oil based concentrate
- More intoxicating than smoking or vaping

Butane Hash Oil Burns

- Names: dabs, wax, earwax, honey, honey oil, shatter
- Contain up to 97% THC
- Products commercially manufactured; some users make them at home
- 20 yo man presented to ED after explosion with burns to face, hands, trunk
- He had been manufacturing hash oil using butane extraction (highly flammable solvent)
- Treated with surgical debridement, pain meds, standard burn care
- Am J Health Syst Pharm 2017;74:1907
Compare Illegal Chemical Structures for JWH-018 and THC - Marijuana Alternatives

- K2, Spice, and related products bear chemical structures that are identical to synthetic cannabinoids, including those with the letters JWH.
- Street drug contains similar to marijuana PLUS sympathetic activity: agitation, anxiety, tachycardia, tremors, seizures, hepatic toxicity. Plus in April 2018 IL & other states incident with rat poison in 94 cases including 2 deaths (brodifacoum).
- Agonists at CB1 and CB2 receptors
- May be NMDA glutamatergic antagonists (like ketamine – euphoria, analgesia)


- Kaiser Permanente Northern California review.
- Questionnaire and tox test within two weeks of questionnaire
- From 2002 to 2014 prevalence of self-reported, past month marijuana use among US adult pregnant women increased from 2.4% to 3.9%
- In aggregated 2002-2012 data, 14.6% of US pregnant adolescents reported past month use
- From 2009 to 2016 adjusted prevalence of prenatal marijuana use based on self report or tox increased from 4.2% (95% CI, 4%-4.5%) to 7.1% (95% CI, 6.7%-7.5%)
- Prenatal marijuana use may impair fetal growth and neurodevelopment despite women’s perception of little to no harm in prenatal use

Endocannabinoids

- Anandamide and 2-AG
- Neural and nonneural cells in injured tissues produce arachidonic acid derivatives called endocannabinoids.
- They modulate neural conduction of pain signals by mitigating sensitization and inflammation through the activation of cannabinoid receptors that are also targeted by delta-9-THC.

Compounds in Cannabis

- Cannabis, like all herbs, is a polypharmaceutical substance.
- 108 cannabinoids have been isolated (recently)
- The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD).
- Minor cannabinoids include cannabidiol, cannabivarin, cannabivarone, and cannabigerol (CGL homolog of THC).
- Terpenoids are common, often aromatic, organic compounds found in many plants. Terpenoids found in cannabis include j–caryophyllene, myrcene, limonene, and pinene.
- As many as 400 other constituents occur in the plant (Turner et al 1965).
Main Phytocannabinoids

- **Psychoactive**: THC (Δ-9-THC, Δ-8-THC, 11-hydroxy-THC [active metabolite]). Binds to CB1 & CB2 receptors as a partial agonist.

- **Not Psychoactive**: THCV (tetrahydrocannabivarin): analogue of THC

Cannabinoid CB1 Receptors

- Mostly in brain (cerebellum, cerebral cortex, basal ganglia), spine, GI tract, liver, pancreas, skeletal muscle combined with GABAergic & dopaminergic & serotonergic receptors; to affect appetite, pain sensation, memory, mood

- In the hippocampus and amygdala, areas associated with partial seizures. CB1 receptors are also present in nociceptive and non-nociceptive sensory neurons of dorsal root ganglion and trigeminal ganglion as well as in defense cells such as macrophages, mast cells, and epidermal keratinocytes.

Cannabinoid CB2 Receptors

- Activation causes inhibition of proinflammatory cytokine production, cytokine, and chemokine release, and blockade of neutrophil and macrophage migration (anti-inflammatory)

- In peripheral immune system T-cells, B cells, spleen, macrophages (immunosuppression), kidneys, lungs

- In peripheral nerve terminals with a role in anti-nociception

Marijuana Use May Raise Risk of Dying from Hypertension

- Three fold risk increase with each additional year of use (NHANES survey); adjusted hazard ratio for death due to hypertension of 3.42 (CI 1.2 – 9.79)

- HR greater than that for current cigarette smokers (HR 1.06; 95% CI 0.4 – 2.77), former smokers (0.33; 95% CI 0.37 – 1.1), alcohol users (HR 0.99; 95% CI 0.37 – 2.49), and those with a prior diagnosis of hypertension (HR 0.81; 95% CI 0.32 – 2.06) or CVD (HR 1.14; 95% CI 0.42 – 0.97)

- Risk may be greater than the risk established for cigarette smoking

- Adults aged 20 and older in survey; N = 1213 (mean age 37.7 years) in cohort
Marijuana/Hashish Bi-Phasic DOSE Effect on Autonomic Nervous System

- LOW DOSES: sympathetic activity is increased while parasympathetic activity is depressed, resulting in mild increases in heart rate and blood pressure
- HIGH DOSES: parasympathetic activity is increased and sympathetic activity is inhibited resulting in the potential for hypotension and bradycardia

Cardiovascular Disorders Associated with ACUTE vs CHRONIC Cannabis Use

- Arrhythmias precipitated by excessive physical activity especially during the first few hours of consumption
- Heterogenous effects on central and peripheral circulation
- Acute cannabis consumption shown to cause increase in BP (SBP) and orthostatic hypotension
- ECS is involved in regulation of heart rate and blood pressure
- THC can cause vasodilation by activating TRP channel, then reflex tachycardia
- Chronic use associated with decrease in HR and disappearance of orthostatic hypotension
- CB2 receptors are expressed in cardiomyocytes, coronary endothelial cells and smooth muscle cells

Cardiovascular Complications

Cannabis use may be associated with:

- Development of atrial fibrillation
- Reversible cerebral vasocstriction syndrome (strong headaches, neurological focal deficit with reversible vasoconstriction)
- Stroke among youth - significantly underestimated
- Synthetic cannabinoids (Spice) can cause tachycardia & other sympathomimetic symptoms


- HOA: reversible vasoconstriction syndrome associated with subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke with MJ use
- MCA Stroke: hypoxia, cerebral vasospasm, arrhythmia associated cardioembolism
- Retrospective cohort analysis, recreational MJ associated with 17% increased likelihood of AIS hospitalization
- Likelihood increased when MJ combined with tobacco use (31%) and with cocaine use (42%)
- Incidence of AIS greater among MJ users compared to non users (RR: 1.13, 95% CI: 1.11-1.15, p = 0.0001) and had greater difference in the 24-34 age group (RR: 2.26, 95% CI: 2.13-2.38, p < 0.0001)


- Cannabis use affects cerebral auto-regulation and vascular tone leading to vasospasm and acute ischemic stroke
- 51 yo female
- PMHx: HTN, asthma, heavy cannabis use
- CC: left upper and lower extremity weakness (2 hours); BP 256/112 mm Hg
- Code stroke called, emergent CT scan of her head without contrast revealed acute right cerebral infarct
- Urine drug screen positive for cannabis
- Treatment: IV heparin, rtPA, marked confusion, slurred speech, repeat CT showed new hemorrhage in left parietal, death
- rtPA decreases platelet aggregation via activating 2-AG, increased cardiac oxygen demand, increases thrombolysis
- THC decreases platelet aggregation via activating 2-AG, increased cardiac oxygen demand, increases thrombolysis
- THB & CBR (brain after 10 minutes but effects on coagulant cascade may last up to 24 hours depending on PT and aPTT)
Impact of Marijuana Use on Patient Care

June 1, 2018


- N = 108 patients, 26% CB+. Delayed cerebral ischemia diagnosed in 50% of CB+ and 24% of urine drug screen negative patients (p = 0.01).
- CB+ independently associated with development of delayed cerebral ischemia (OR, 2.68; 95% CI, 1.03-6.99; p = 0.04). Significantly higher number of CB+ than urine drug screen negative patients had poor outcomes (39.7% vs 13.8%; p < 0.01).
- Univariate analysis: CB+ associated with composite and separate endpoint of hospital mortality/severe disability (OR, 2.53; 95% CI, 1.03-6.01; p = 0.04).
- After adjustment for other predictors, this effect was no longer significant.
- Preliminary Conclusion: CB+ is independently associated with delayed cerebral ischemia and possibly poor outcome in patients with aSAH.

CANNABIS
Drug Interactions
Cytochrome P450 Enzymes

- THC and CBD are metabolized by CYP1A2 and CYP2C9 (Manuel et al. 2003, Yamasaki et al. 2007).
- CYP3A4 inhibitors slightly increase THC levels.
- CYP3A4 inducers slightly decrease THC and CBD levels.
- CBD, but not THC, is metabolized by CYP2C9 (Stav and Cunha 2014).

Cannabis/Drug Interactions & Effects

- May interact with warfarin (THC and CBD increase warfarin levels) (Yamasaki et al. 2007).
- Increases bleeding when used with anticoagulants (warfarin, Xarelto, Eliquis), antiplatelet agents (Plavix, Brilinta), NSAIDs (Celebrex, Motrin, Aleve, ASA).

CANNABIS
Patient Scenarios

Psychiatric and Medical Management of Marijuana Intoxication in the EMR Dept
Impact of Marijuana Use on Patient Care

June 1, 2018

Patient #1

- 34yo female who recently gave birth and is lactating
- CC: racing thoughts, insomnia, euphoria x 1 week
- Disruptive behavior psychotic symptoms after recreational marijuana edible cannabis (THC). Auditory hallucinations. “Broke into neighbor’s home requesting to go to heaven. Feared people were stealing from her and that something bad was going to happen.”
- Social History: Adopted
- Illicit Drug History: recreational cannabis lip balm, cannabis chocolate bars, cannabis dabbing daily over past week

Labs/Diagnostic Tests:
- $K^+ = 3.2 \text{ mg/dL}$
- 12-Lead EKG: QTcB interval = 508 msec
- Temp = 97.5F; HR = 96
- BP = 148/111; Resp Rate = 11
- Random BS = 196
- 9-carboxy-THC Blood Level - over 500 ng/mL
- Unremarkable CT head
- Unremarkable CBC

PTA OTC/Meds:
- Energy drinks (+ coffee)
- Propranolol 20 mg po BID for hypertension
- Sumatriptan 50 mg po PRN migraines
- Feverfew 100 mg po daily migraine prevention
- Benadryl 25 mg po HS PRN sleep
- Imodium (loperamide) po at higher than package recommended dose of 8 mg/day (euphoria)

Diagnosis: Marijuana-induced psychotic disorder, Marijuana use disorder

Workup:
- Check co-ingestion of other medications (positive urine tox screen for opioids)
- Check coffee consumption - via mesolimbic dopamine activity, caffeine may precipitate psychosis or worsen affective lability and mood states
- EKG - tele monitor (checking DI with cannabis/propranolol)

Patient #1 Treatment

- Treat hypokalemia and blood sugar excursions
- Risperidone 0.5 mg q 6 h and lorazepam 1 mg q6 h for psychosis and anxiety, respectively
- DC coffee & energy drinks (caffeine)
- Opioid Detox Program - 72 hours in hospital. Warm referral to addiction management center for MAT therapy; Lactation consultant for alternatives
- DC Imodium (prolonged QTcB) on discharge MedRec
Impact of Marijuana Use on Patient Care

Peri-Op Implications of Cannabis Use

- Important to obtain complete illicit drug use history and confirmatory tests if suspected before surgical intervention
- Significant respiratory symptoms and changes in spirometry
- Avoid CNS depressants like barbiturates, opioids, benzos, phenothiazines
- Avoid drugs that increase HR like ketamine, atropine, epinephrine
- Intra-op and immediate post-op need of opioids for analgesia in patients with history of recent or chronic cannabis consumption may be significantly increased

Propofol Induction

- Prospective, randomized, single blind study
- N = 30 males using cannabis > once/week; N = 30 nonusers
- Primary outcomes: Propofol ED50 and successful induction determined by loss of consciousness with bispectral index (BIS) value > 60 and insertion of laryngeal mask
- Results: Propofol dose needed to achieve target BIS value not significantly higher in user group, but this group needed significantly higher propofol dose to insert laryngeal mask (314.9 mg ± 109.3 mg vs 263.2 mg ± 69.5 mg, p < 0.04)
- Limitation: no blood level of cannabinoids measured for users

Cannabis use increases propofol dose required to insert laryngeal mask


- Prospective, randomized study
- N = 30 males using cannabis > once/week; N = 30 nonusers
- Primary outcomes: Propofol ED50 and successful induction determined by loss of consciousness with bispectral index (BIS) value > 60 and insertion of laryngeal mask
- Results: Propofol dose needed to achieve target BIS value not significantly higher in user group, but this group needed significantly higher propofol dose to insert laryngeal mask (314.9 mg ± 109.3 mg vs 263.2 mg ± 69.5 mg, p < 0.04)
- Limitation: no blood level of cannabinoids measured for users

Cannabis use increases propofol dose required to insert laryngeal mask


- Prospective, randomized study
- N = 40 cannabis users (based only on history)
- N = 31 non-users
- All: elective ortho surgery, received Demerol
- Primary Outcome: Mean pain intensity difference at the first postop hour (MPID1) and sum of pain intensity differences (SPID1)
- Results: Users had significantly higher supplemental Demerol requirements (46.2 mg, SD = 15.4 vs 30.6 mg, SD = 22.7, p = 0.016) and significantly greater MPID1 scores (2.7, SD = 1.29 vs 1.35, SD = 1.12, p = 0.001) compared to non-users
- Female users required significantly more analgesic than males (49.3 mg, SD = 40.9 mg vs 76.9 mg, SD = 44.5, p = 0.025)
- Conclusions: Greater demand of rescue opioid analgesia within first 6 hours after surgery

Female users required significantly more analgesic than males
Types of Pain

- Visceral, neuropathic, somatic, bone
- IN-PATIENT MULTI MODAL PAIN TREATMENT: APAP, topical NSAIDs, gabapentin, pregabalin, antidepressants, aromatherapy, acupuncture, narcotics, ginger cream, lidocaine patch

Pain Origins (Objective vs Subjective Responses)

- Nociceptive pain - damage to body tissue (sharp, aching, throbbing). Invading immune cells secrete histamine, serotonin, bradykinin, prostanoids, tumor necrosis factor alpha, interleukin 1 beta, interleukin 6, interleukin 17. Signals carried by C and A gamma peripheral nerves to demal root ganglia to thalamus to cortical area.
- Neuropathic pain - damage to sensory or spinal nerves sending inaccurate pain messages to higher centers. Diabetic neuropathy. SUBJECTIVE
- Centralized pain - results from amped peripheral signals. Pain persists despite lack of clear peripheral cause. Fibromyalgia. SUBJECTIVE

Marijuana and Pain Management

- Subjective?
  - There is no way to calculate an equi-analgesic dose of opioid to supplant any marijuana used prior to surgery even though there is a cannabis conversion table for different dose forms
  - Surgical anesthesia may be more complex in recent cannabis users with reports of more difficulty with sedation and induction of anesthesia

Pain Management

- APAP 650 mg po q 4h PRN mild pain (1-3) or fever
- Tramadol 50 mg po q 4h PRN moderate pain (4-6)
- Dilaudid 0.5 – 1 mg IV q 4h PRN severe pain (7-10)
- Dilaudid 4 mg po q 4h PRN severe pain (7-10)
- Xanax 0.25 mg BID after HD
- Nystatin, Neosporin, Mupirocin, Icy Hot products

Patient #2 - 70 yof 5'3" 223#

- Social Hx: Recreational marijuana, 2 joints smoked daily (neuropathic pain)
- Labs: FBS = 124 (70-99 mg/dL)
- Na = 138 (135-145 mEq/L)
- K = 4.6 (3.6 – 5.1 mEq/L)
- Cl = 99 (101-111 mEq/L)
- BUN = 21 (8-26 mg/dL)
- Cr = 6.6 (0.4 – 1 mg/dL)
- Calcium = 4.2 (4.6 – 5.4 mg/dL) ionized
- CC: Foot ulcer (debride)
- Allergies: Morphine (confusion) Percocet (itch)
- PMHx: CHF, non STEMI, CAD, PCI-stent, S/P CABG x 2, high cholesterol, DM Type 1, ESRD on dialysis HWF, HTN, PAD, Diabetic Foot Ulcer/ Osteomyelitis, Peripheral Neuropathy, Anxiety

Patient #2 PTA Meds:
- Coreg 6.25 mg BID
- Lipitor 80 mg q HS
- Neurontin 100 mg TID
- Xanax 0.25 mg BD PAIN anxiety after HD
- Levetiracetam morning daily
- Epogen 3200 units daily HbP only (anemia)
- Sevelamer 2450 mg TID with meals (phosphate binder)
- Minax PRN

New Meds:
- Venclextin 1 gram IV x 1
- Celecoxib 2 grams IV daily HFP only
- APAP 600 mg po q 4h PRN mild pain (1-3) or fever
- Tramadol 50 mg po q 4h PRN moderate pain (4-6)
- Dilaudid 0.5 - 1 mg IV q 4h PRN severe pain (7-10)
- Dilaudid 4 mg po q 4h PRN severe pain (7-10)
- Propofol, Versed, mepivacaine 2% to debride foot wound

Patient #2 New Meds:
- Morphine, Vicodin, Percocet *intolerances/allergies*

Classes of Opioid Medications

Phenanthrenes
- Codeine
- Hydrocodone
- Hydromorphone
- Levoelephine
- Meperidine
- Oxycodone

Phenanthrene Analgesics
- Naltrexone
- Pentazocine
- Pentazocine

Phenanthrene Binders
- Naltrexone
- Fentanyl
- Iloperidine

Other Translates

*Independent is not recommended for chronic pain because of the potential for accumulation of the associated metabolite, N-demethylation, and a potentially toxic dimer interaction with neurocystic acid inhibition (MAO).*

Impact of Marijuana Use on Patient Care

June 1, 2018

CPFI Annual Meeting, Bonclarken
Patient #2 - Cannabis/Drug Interactions

- Cardiovascular - CBD and Coreg increased [ ]. Monitor EKG, BP? THC cardiovascular side effects of long term use?

- Pain/Anxiety - CBD and increased [ ] Opioids, increased Xanax [ ]. Monitor pain med dosing?

Patient #2 (Treatment)

- Pain management (debridement): - Propofol dosing increase? - Address benzos and opioids together - DC Dilaudid, keep tramadol (acute) - Other modalities for chronic pain?

- Hemodialysis effects on THC removal from the blood:
  - None as THC metabolites are lipid soluble, not water soluble

Patient #2 Discharge MedRec

- Marijuana for diabetic foot ulcer/peripheral neuropathy pain
- Anxiety about hemodialysis and the future

Admission MedRec Process

Medication Reconciliation

Medication discrepancy: A difference between medication regimens derived from various sources (e.g., medical records and patients’ home medication lists).
- Intentional discrepancy: A medication prescribed differently from the patient’s original medication order due to the patient’s current health status (e.g., the reduced dosage of the antihypertensive agent due to patient’s hypotensive state).
- Unintentional discrepancy: A medication prescribed differently from the original medication order without a documented reason.
Motivational Interviewing (Miller & Rollnich)

- Person-centered, goal-oriented methods of communication for eliciting and strengthening intrinsic motivation for change
- Provider patient relationships characterized by PACE: partnership, acceptance, compassion, and evocation (drawing out of patients their own internal reasons for change)
- Open-ended questions, affirmations, reflections, summaries
- SEEK FIRST TO UNDERSTAND
- www.motivationalinterviewing.org

Medical Marijuana Policy Development

- Hospital Inpatient Policy: Pharmacist-Led Medication Reconciliation
- Computer Documentation: “social history” versus “medication”
- Storage, chain of evidence/log, employee FMLA usage, random drug screens, education (interactions), management of outpatient MD certification requests
- SOAP notes

Impact of Marijuana Use on Patient Care: From Recreation to Reconciliation

CPFI 2018 Conference
Bonclarken Conference Center
Flat Rock, North Carolina
Cathy Rosenbaum PharmD MBA RPh CHC
Founder & CEO, Rx Integrative Solutions
Loveland OHIO

Copyright 2018

Thank You