

Young-Wolff. Trends in Self-Reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016. JAMA 2017: 318:2490.

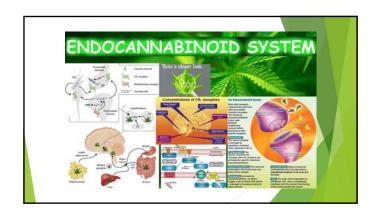
It kalser Permanente Northern California review. Questionnaire and tox test within two weeks of questionnaire

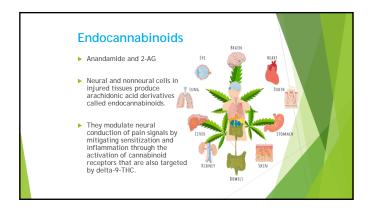
From 2002 to 2014 prevalence of self-reported, past month marijuana use among US adult pregnant women increased from 2.4% to 3.9%

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% Cl. 44.-5%) to 7.1% (95% I, 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







Main Phytocannabinoids



- Psychoactive: THC (Δ-9-THC, Δ-8-THC, 11hydroxy-THC [active metabolite]). Binds to CB1 & CB2 receptors as a partial agonist.
- ► Not Psychoactive: THCV (tetrahydrocannabivarin):analogue of THC

Main Phytocannabinoids



Not Psychoactive:

- ► CBD (cannabidiol)
- ▶ CBN (cannabinot) degradation product of THC
- ▶ CBC (cannabichromene) sedative and analgesic
- ▶ CBG (cannabigerol) precursor of other cannabinoids

Cannabinoid CB1 Receptors



- Mostly in brain (cerebellum, cerebral cortex, basal ganglia), spine, GI tract, liver, pancreas, skeletal muscle combined with GABAergic & dopaminergic & serotoninergic receptors; to affect appetite, pain sensation, memory, mood
- ▶ In the hippocampus and amygdala, areas associated with partial seizures. CBI 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 <u>inhibition</u> 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 **antinociception**

Side

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 (Cl 1.2 9.79)
- ► HR greater than that for current cigarette smokers (HR 1.06; 95% CI 0.4 2.77), former smokers (1.33; 95% CI 0.57 3.1), alcohol users (HR 0.95; 95% CI 0.37 2.45), and those with a prior diagnosis of hypertension (HR 0.81; 95% CI 0.32 2.06) or CVD (HR 1.94; 95% CI 0.42 8.97)
- ▶ 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

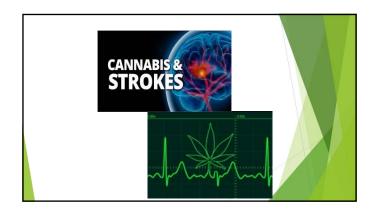
Cardiovascular Disorders Associated with ACUTE vs CHRONIC Cannabis Use

- 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 TRPA-1 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 vasoconstriction syndrome (strong headaches, neurological focal deficit with reversible vasoconstriction)
- ▶ Stroke among youth significantly underestimated
- ▶ Synthetic cannabinoids (Spice) can cause tachycardia & other sympathomimetic symptoms



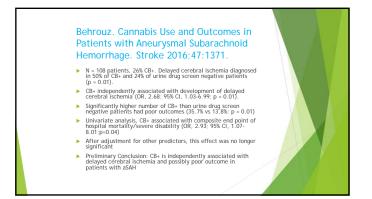
Recreational MJ Use & Acute Ischemic Stroke (AIS): A Population Analysis of Hospitalized Patients in the US. J Neurol Sci 2016;364:191

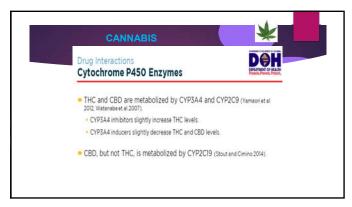
- MOA: reversible vasoconstriction syndrome associated with subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke with MJ use
- MOA Stroke: hypotension, cerebral vasospasm, arrhythmia associated cardioembolism
- Retrospective cohort analysis, recreational MJ associated with 17% increased likelihood of AlS 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% Cl: 1.11-1.15, p < 0.0001) and had greatest difference in the 24-34 age group (RR: 2.26, 95% Cl: 2.13-2.38, p < 0.0001)</p>

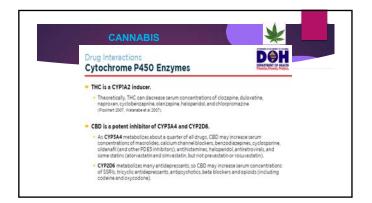
Shere. Cannabis Can Augment Thrombolytic Properties of rtPA: Case Report of Intracranial Hemorrhage in a Heavy Cannabis User. Am J Emer Med 2017.

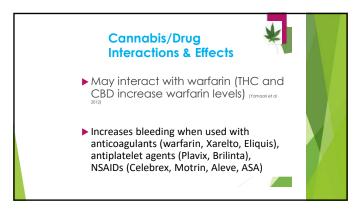
- ▶ 51 vo female
- PMHx: HTN, asthma, heavy cannabis use
 CC: left upper and lower extremity weakness (2 hours); BP 256/112 mm Hg
- Code stroke called, emergent CT scan of her head without contrast revealed acute right cerebral infarct
- Urine drug screen positive for cannabis
- Treatment: VI labetaloi, 17IA. Marked confusion, slurred speech, repeat CT showed new hemorrhage in left pors, death

 Ht decrease platelet aggregation via activating 2-AG, increased cardiac oxygen demand, vasoconstriction
- ► CB1 & CB2 receptors on platelets
- rtPA is 80% cleared after 10 minutes but effects on coagulation cascade may last up to 24 hours (prolongs PT and aPTT)

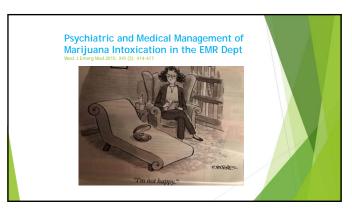




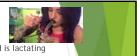








Patient #1



- 34yof 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

Patient #1

Labs/Diagnostic Tests:



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

Patient #1



► 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

Patient #1



- Chronic marijuana users have lower serum sodium and potassium than non users
- Heavy consumption of carbs while intoxicated leads to increase in serum insulin levels driving potassium into cells and causing serum hypokalemia
- Hypokalemia produces reentrant arrhythmias by decreasing conductivity and increasing resting membrane potential, duration of action potential, and duration of the refractory period
- ▶ May see periodic hypokalemic paralysis
- ▶ EKG changes include decrease in T wave amplitude, presence of U waves, and prolonged QTcB (THC or Imodium)

Patient #1 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 MedRe



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 opiates for analgesia in patients with history of recent or chronic cannabis consumption may be significantly increased



Flisberg. Induction Dose of Propofol in Patients Using Cannabis. Euro J Anaesthesiology 2009;26:192.

- ▶ 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)</p>
- ► Limitation: no blood level of cannabinoids measured for users
- Cannabis use increases propofol dose required to insert laryngeal mask

Jefferson. Postoperative Analgesia in the Jamaican Cannabis User. J Psychoactive Drugs 2013;45:227.

- ▶ Prospective, randomized study
- N = 42 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)
- (SrID1)

 Results: Users had significantly higher supplemental Demerol requirements (82.7 mg, SD = 4.4 vs.51.6 mg, SD = 42.7, p = 0.003) and significantly greater MPID1 scores (1.88, SD = 1.09 vs. 1.35, SD = 1.12, p = 0.001) compared to non users
- Female users required significantly more analgesic than males (93.3 mg, SD = 45.8 mg vs 78.3 mg, SD = 44.3, p = 0.025)
- Conclusions: Greater demand of rescue opioid analgesia within first 6 hours after surgery



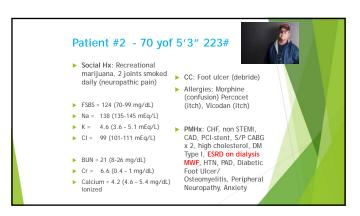




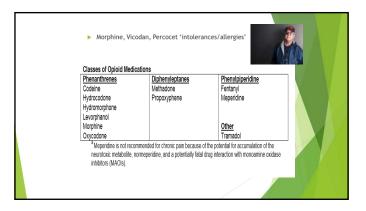
Pain Origins (Objective vs Subjective Responses)

- ▶ Nociceptive pain damage to body tissue (sharp, aching, throbbing). Invading immune cells secrete histamine, serotonin, bradykinin, prostaglandin, tumor necrosis factor alpha, interleukin 1 beta, interleukin 6, interleukin 17. Signals carried by C and A gamma peripheral nerves to dorsal 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









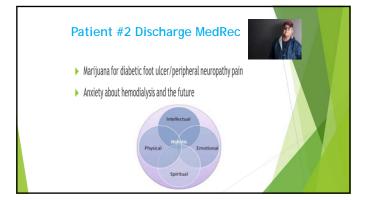
Patient #2 - Cannabis/Drug Interactions

- ➤ 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?

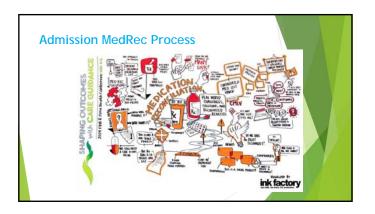


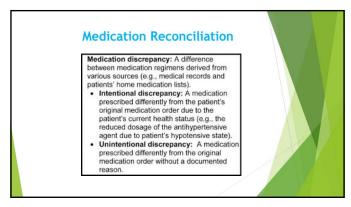
Patient #2 (Treatment)

- ▶ 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,











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

