Updated Guidelines on the Perioperative Management of Cannabinoids

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Financial Disclosures

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- Content Expert for UptoDate on Substance Use and Anesthesia

Learning Objectives

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- Participants should be able to:
  - Quantify prevalence of cannabinoid use
  - Understand the mechanism of action of cannabinoids
  - Identify recommendations for perioperative management

Disclaimer

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Prevalence of Use

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Table 1.1A Types of Illicit Drug Use in Lifetime, Past Year, and Past Month: Among People Aged 12 or Older; Numbers in Thousands, 2021

Drug	Lifetime (2021)	Past Year (2021)	Past Month (2021)
ILLICIT DRUGS[1]	138,790	61,203	39,995
Marijuana	128,016	52,454	36,363
Cocaine	40,901	4,765	1,833
Crack	10,640	996	527
Heroin	6,635	1,099	589
Hallucinogens	45,826	7,406	2,234
LSD	29,502	2,477	524
PCP	6,464	183	96
Ecstasy	21,122	2,199	594
Inhalants	25,596	2,178	830
Methamphetamine	16,830	2,549	1,617
Misuse of Prescription Psychotherapeutics	nr	14,284	4,263
Pain Relievers	nr	8,711	2,401
Stimulants	nr	3,733	1,104
Tranquilizers or Sedatives	nr	4,887	1,373
Tranquilizers	nr	4,317	1,184
Sedatives	nr	923	227
Benzodiazepines	--	3,941	--
Opioids	nr	9,236	2,791
Central Nervous System Stimulants	nr	9,177	4,126
Illicit Drugs Other Than Marijuana[2]	nr	23,249	9,030

Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2021 national survey on drug use and health

What about Pediatrics?

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Table 1.2A Types of Illicit Drug Use in Lifetime, Past Year, and Past Month: Among People Aged 12 to 17; Numbers in Thousands, 2021

Drug	Lifetime (2021)	Past Year (2021)	Past Month (2021)
ILLICIT DRUGS[1]	5,549	3,662	1,844
Marijuana	3,423	2,724	1,499
Cocaine	102	40	5
Crack	16	3	*
Heroin	6	*	*
Hallucinogens	591	347	78
LSD	419	249	41
PCP	30	20	4
Ecstasy	146	92	9
Inhalants	2,294	626	205
Methamphetamine	50	37	14
Misuse of Prescription Psychotherapeutics	nr	851	200
Pain Relievers	nr	497	115
Stimulants	nr	304	74
Tranquilizers or Sedatives	nr	225	44
Tranquilizers	nr	198	28
Sedatives	nr	41	19
Benzodiazepines	--	181	--
Opioids	nr	497	115
Central Nervous System Stimulants	nr	339	92
Illicit Drugs Other Than Marijuana[2]	nr	1,562	476

Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2021 national survey on drug use and health

Legal Medical & Recreational Marijuana States

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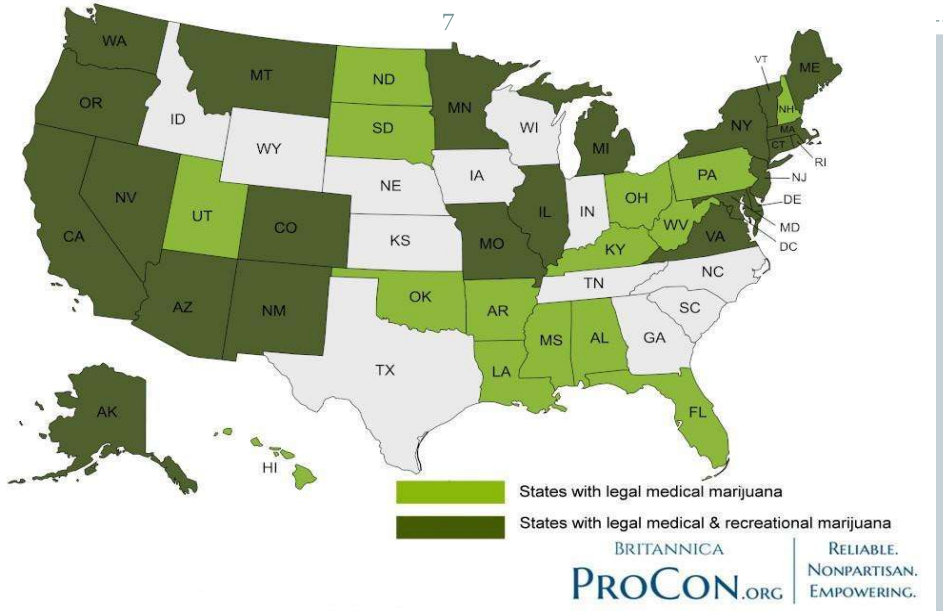

As of August 1, 2023!

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Cannabinoids

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THC

- Psychoactive
  - Intoxication

CBD

- Anti-inflammatory, Anti-epileptic

Endocannabinoid System

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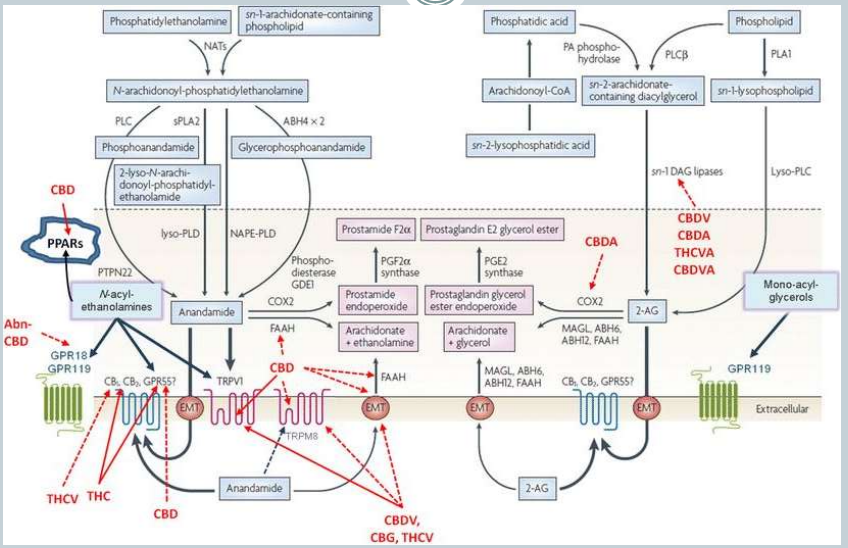

Di Marzo V et al. *Neurotherapeutics*, 2015

To Simplify

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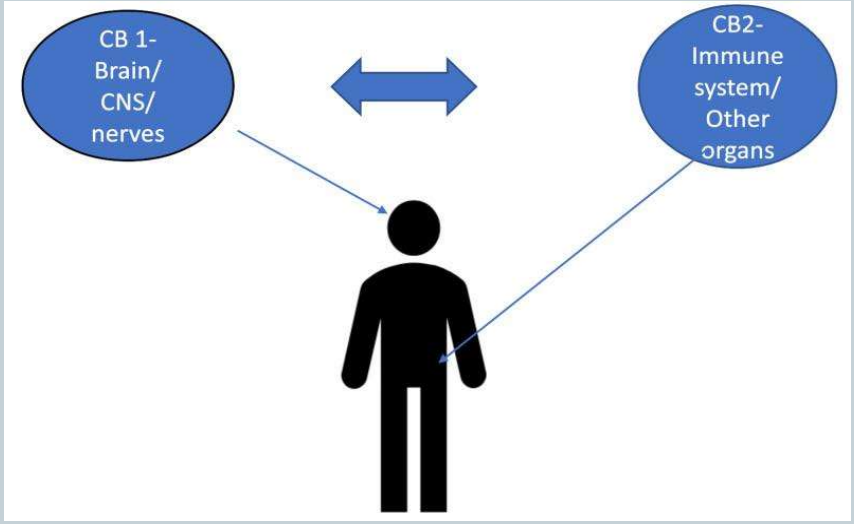

Anthony AT et al. *Cureus*, 2020

Δ9-Tetrahydrocannabinol (THC)

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- Mechanism of Action
  - Partial Agonist for Cannabinoid Receptor 1
    - Active voltage-gated potassium channels -> inhibit NT release
      - Mediates psychoactive properties: memory, consciousness, mood
- Usage
  - Route: inhalation, oral, sublingual, transdermal
  - Inhalation produces rapid absorption + shorter ½ life
  - Metabolized by CYP enzymes -> potential for drug interactions

Cannabinol (CBD)

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- Mechanism of Action
  - Weak inverse agonist of CB1 receptor
    - Anti-inflammatory effect
  - Seratonin 1A, Vanilloid receptor 1, Adenosine A2A receptors
    - Regulate perception of pain
- Pharmacokinetics
  - Route: inhalation, oral, sublingual, transdermal
  - Metabolized by CYP enzymes -> potential for drug interactions
  - Oral ½ life is 2-5 days

Sense of timing

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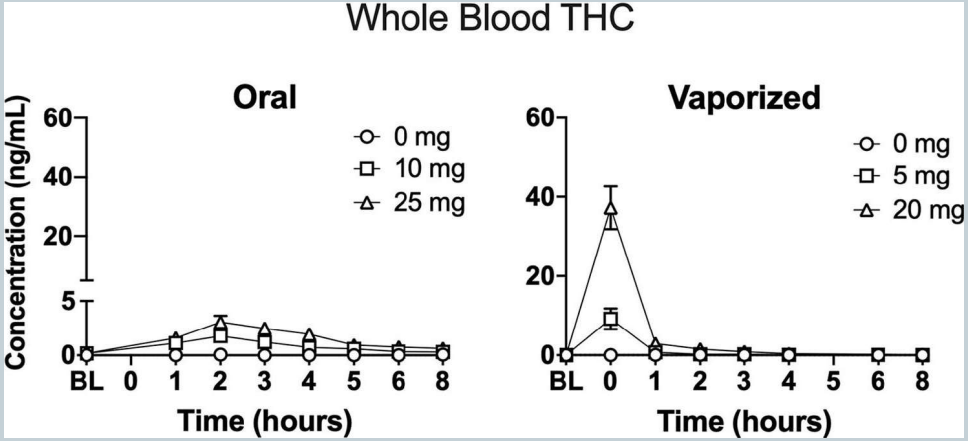

Spindle TR et al. *J Psychopharmacol*, 2022

Concerning Drug-Drug Interactions

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Table 2 Cannabinoid drug Interactions with anticoagulants and antiplatelets used with permission from Samer Narouze, MD, PhD [60–62]

Cannabinoids drug interactions with anticoagulants and antiplatelets		
Drug	**Effect**	**Intervention**
Warfarin	THC and CBD can cause competitive inhibition of CYP2C9 and inhibit metabolism of the S-warfarin isomer, leading to supratherapeutic international normalized ratio levels.	▶ Check INR within 3 days
DOACs (direct-acting oral anticoagulants)	CBD and possibly THC can increase DOACs level due to competitive inhibition of P-glycoproteins, and to a lesser extent CYP3A4.	▶ Close monitoring ▶ Consider using other anticoagulants or discontinue CBD/THC
Clopidogrel	CBD and possibly THC can increase clopidogrel level due to the competitive inhibition of CYP2C19.	▶ Consider using another antiplatelet
Heparin/fondaparinux	No known interactions as these agents are processed by endothelial and renal cells and not metabolized by CYP enzymes, UGT, or P-glycoprotein.	
Platelets	Immune thrombocytopenia with synthetic cannabis.	▶ Unlikely to have significant clinical effects ▶ Immune thrombocytopenia is rare

CBD, cannabidiol; THC, tetrahydrocannabinol.

Shah S et al. *Reg Anesth Pain Med*, 2023

Cannabis Perioperative Consequences

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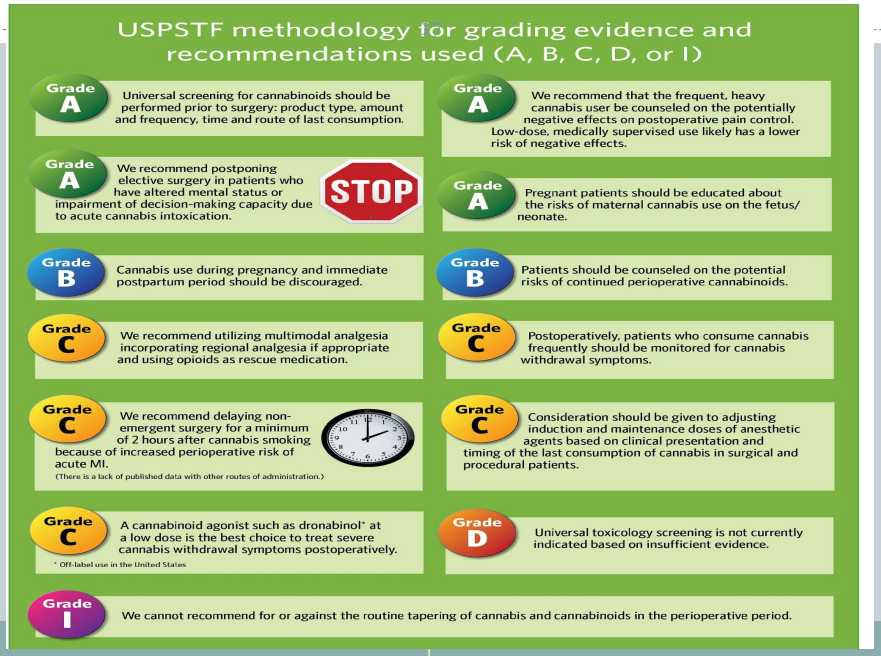
- Cognitive Impairment
  - Driving-related cognitive skills using *20 mg THC*
    - *Inhaled = 5 hours*
    - *Ingested = 8 hours*
- Cardiovascular (Biphasic)
  - Acute Use = Hypertension, Tachycardia
    - Increased risk of MI
  - Chronic Use = Hypotension, Bradycardia
- Pulmonary?
- GI
  - Increased PONV
- Analgesia
  - Worsened postoperative pain
  - Increased opioid use
- Anesthesia
  - Acute Use = Decreased MAC
  - Chronic Use = Increased MAC

McCartney D et al. *Neurosci Biobeh Rev*, 2021

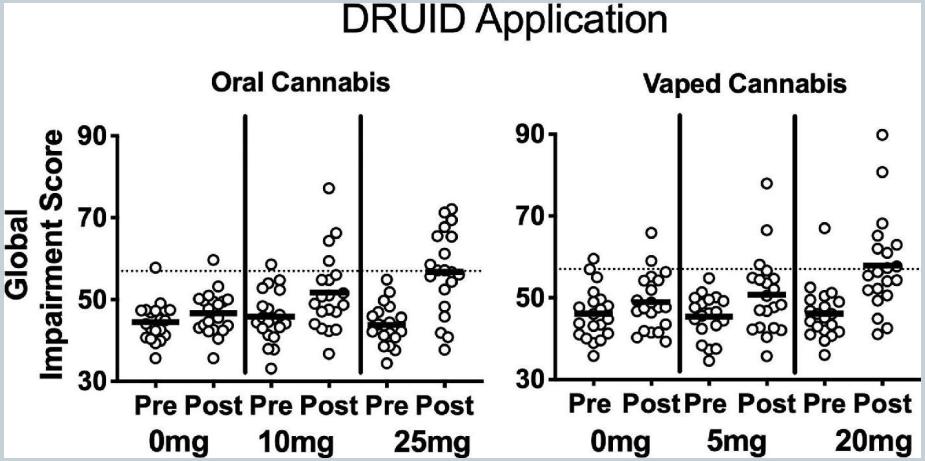
Recommendations



Level A Recommendations

- Determine dose/frequency/route of cannabis use
- Postpone elective surgery if patient is acutely intoxicated
- May be an association with cannabis use and poor postoperative pain
- There are potential risks to fetus in the setting of maternal cannabis use

Impairment by Dosing



Spindle TR et al. *J Psychopharmacol*, 2022

Formal Testing?

- Many applications available (mostly commercial)
  - An Example of 4 Tasks
    - Decision Making/Reaction Time
    - Time Estimation and Reaction Time
    - Hand-Eye Coordination
    - Balance

What about pain?

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- 8 randomized trials + 4 observational studies (>4000 patients) observing acute pain

Table 3 Secondary outcome results

Outcome	Number of included studies	Cannabinoid mean (SD) or n/N	Control mean (SD) or n/N	Mean difference or OR (95% CI)	P value for statistical significance	P value for heterogeneity	I^2 test for heterogeneity	Quality of evidence (GRADE)
*Randomized trials**								
Rest pain at 1 hour (PACU) (cm)	7	3.14 (3.04)	2.96 (3.06)	0.17 (-0.60 to 0.94)	0.67	<0.00001	86%	⊕⊕⊕⊖
Rest pain at 6 hours (cm)	6	3.91 (2.83)	3.84 (2.79)	0.11 (-0.77 to 0.99)	0.81	<0.00001	89%	⊕⊕⊕⊖
Rest pain at 12 hours (cm)	3	3.62 (2.54)	2.79 (2.49)	0.83 (0.04 to 1.63)	0.04	0.03	71%	⊕⊕⊕⊖
Oral morphine consumption at 2 hours (PACU) (mg)	3	18.36 (24.33)	17.83 (18.46)	1.12 (-4.71 to 6.94)	0.71	<0.0001	91%	⊕⊕⊕⊖
Oral morphine consumption at 24–48 hours (mg)†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quality of recovery†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Patient satisfaction (cm)†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Opioid-related side effects†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abdullah FW et al. *Reg Anesth Pain Med, 2020*

OB Consequences

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- Fetal
  - Readily crosses the placenta
    - Associated with altered neurodevelopment and prematurity
      - CB1 receptors are present at 14 weeks and increase with GA
        - Prenatal cannabis use associated with:
          - Decreased problem solving + attention span
          - Increased behavioral problems
- Maternal
  - Hyperemesis syndrome
  - Increased postoperative hypothermia
  - Small amounts can be transmitted in breast milk (2.5%)
    - Can remain in breastmilk for up to 1 week

Gunn JKL et al. *BMJ Open, 2016*

Recommendations

USPSTF methodology for grading evidence and recommendations used (A, B, C, D, or I)

- **Grade A** — Universal screening for cannabinoids should be performed prior to surgery: product type, amount and frequency, time and route of last consumption.
- **Grade A** — We recommend that the frequent, heavy cannabis user be counseled on the potentially negative effects on postoperative pain control. Low-dose, medically supervised use likely has a lower risk of negative effects.
- **Grade A** — We recommend postponing elective surgery in patients who have altered mental status or impairment of decision-making capacity due to acute cannabis intoxication. STOP
- **Grade A** — Pregnant patients should be educated about the risks of maternal cannabis use on the fetus/neonate.
- **Grade B** — Cannabis use during pregnancy and immediate postpartum period should be discouraged.
- **Grade B** — Patients should be counseled on the potential risks of continued perioperative cannabinoids.
- **Grade C** — We recommend utilizing multimodal analgesia incorporating regional analgesia if appropriate and using opioids as rescue medication.
- **Grade C** — Postoperatively, patients who consume cannabis frequently should be monitored for cannabis withdrawal symptoms.
- **Grade C** — We recommend delaying non-emergent surgery for a minimum of 2 hours after cannabis smoking because of increased perioperative risk of acute MI. (There is a lack of published data with other routes of administration.)
- **Grade C** — Consideration should be given to adjusting induction and maintenance doses of anesthetic agents based on clinical presentation and timing of the last consumption of cannabis in surgical and procedural patients.
- **Grade C** — A cannabinoid agonist such as dronabinol* at a low dose is the best choice to treat severe cannabis withdrawal symptoms postoperatively. * Off-label use in the United States.
- **Grade D** — Universal toxicology screening is not currently indicated based on insufficient evidence.
- **Grade I** — We cannot recommend for or against the routine tapering of cannabis and cannabinoids in the perioperative period.

Level B Recommendations

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- Refrain from using cannabis during pregnancy and immediately postpartum
- There are risks to continued perioperative use of cannabis

Recommendations

USPSTF methodology for grading evidence and recommendations used (A, B, C, D, or I)

- **Grade A** — Universal screening for cannabinoids should be performed prior to surgery: product type, amount and frequency, time and route of last consumption.
- **Grade A** — We recommend that the frequent, heavy cannabis user be counseled on the potentially negative effects on postoperative pain control. Low-dose, medically supervised use likely has a lower risk of negative effects.
- **Grade A** — We recommend postponing elective surgery in patients who have altered mental status or impairment of decision-making capacity due to acute cannabis intoxication. STOP
- **Grade A** — Pregnant patients should be educated about the risks of maternal cannabis use on the fetus/neonate.
- **Grade B** — Cannabis use during pregnancy and immediate postpartum period should be discouraged.
- **Grade B** — Patients should be counseled on the potential risks of continued perioperative cannabinoids.
- **Grade C** — We recommend utilizing multimodal analgesia incorporating regional analgesia if appropriate and using opioids as rescue medication.
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- **Grade D** — Universal toxicology screening is not currently indicated based on insufficient evidence.
- **Grade I** — We cannot recommend for or against the routine tapering of cannabis and cannabinoids in the perioperative period.

Level C Guidelines

- Incorporate a multimodal analgesic plan, using opioids as rescue medication
- Delay non-urgent surgery for 2 hours after inhaled cannabis
- Chronic cannabis users should be monitored for cannabis withdrawal symptoms and potentially treated with dronabinol
- May need to adjust anesthetic based on chronic or recent usage

Postoperative MI?

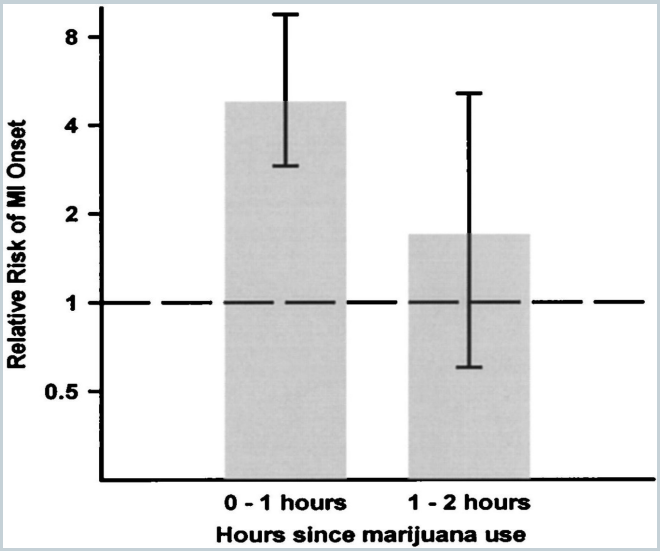
	Unadjusted Analyses				Adjusted Analyses			
	Cannabis Use Disorder (n = 13,603)	No Cannabis Use Disorder (n = 4,172,619)	Odds Ratio, Length of Stay Ratio, or Total Cost Ratio (95% CI) (Cannabis Use Disorder *vs.* No Cannabis Use Disorder)	*P* Value	Cannabis Use Disorder (n = 13,603)	No Cannabis Use Disorder (n = 13,603)	Odds Ratio, Length of Stay Ratio, or Total Cost Ratio (95% CI) (Cannabis Use Disorder *vs.* No Cannabis Use Disorder)	*P* Value
Primary composite outcome (%)	405 (2.98)	97,020 (2.33)	1.29 (1.17 to 1.42)	< 0.001	400 (2.9)	415 (3.1)	0.97 (0.84 to 1.11)	0.631
Myocardial infarction (%)	89 (0.64)	9,523 (0.23)	2.88 (2.34 to 3.55)	< 0.001	89 (0.7)	46 (0.3)	1.88 (1.31 to 2.69)	< 0.001
Respiratory failure (%)	165 (1.21)	34,451 (0.83)	1.47 (1.26 to 1.72)	< 0.001	163 (1.2)	179 (1.3)	0.91 (0.74 to 1.13)	0.396
Acute kidney injury (%)	162 (1.19)	49,225 (1.18)	1.01 (0.86 to 1.18)	0.905	161 (1.2)	179 (1.3)	0.90 (0.72 to 1.11)	0.310
VTE (%)	26 (0.19)	9,997 (0.24)	0.80 (0.54 to 1.17)	0.291	25 (0.2)	38 (0.3)	0.68 (0.41 to 1.13)	0.134
Sepsis (%)	46 (0.34)	12,370 (.30)	1.14 (0.85 to 1.53)	0.344	45 (0.3)	55 (0.4)	0.83 (0.56 to 1.23)	0.360
CVA (%)	17 (0.12)	2,595 (0.06)	2.01 (1.25 to 3.24)	0.008	17 (0.1)	NR	3.30 (1.22 to 8.96)	0.019
Mortality (%)	12 (0.09)	3,646 (0.09)	1.01 (0.57 to 1.78)	0.884	12 (0.1)	14 (0.1)	0.87 (0.40 to 1.88)	0.719
Length of stay, days (95% CI)	3.61 (3.57 to 3.65)	3.29 (3.29 to 3.29)	1.10 (1.01 to 1.11)	< 0.001	N/A	N/A	0.99 (0.97 to 1.00)	0.148
Total cost, USD (95% CI)	13,100 (12,932 to 13,269)	12,450 (12,441 to 12,459)	1.05 (1.04 to 1.07)	< 0.001	N/A	N/A	1.01 (0.99 to 1.03)	0.159

Cell sites less than or equal to 10 cannot be published as per the data use agreement of the Nationwide Inpatient Sample. Survey weights were not used in this analysis. Significance defined as $P < 0.05$ for the composite outcome and $P < 0.005$ for the secondary outcomes. Results were obtained using regression models after adjusting for confounders. CVA, cerebrovascular accident; N/A, not applicable; NR, not reportable; USD, United States dollars; VTE, venous thromboembolism.

Goel A et al. *Anesthesiology, 2020*

Why 2 hours?

- 3882 patients
  - 124 used THC
    - 37 w/in 24 hours
    - 9 w/in 1 hour



Mittleman MA et al. *Circulation,* 2001

Cannabis Withdrawal Syndrome

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- This is generally a ***THC*** problem, not a CBD one
- Diagnosis
  - >3 of the following symptoms:
    - Irritability/anger
    - Anxiety
    - Insomnia
    - Decreased appetite
    - Physical discomfort (abd pain, headache, sweating, tremors, chills)
- Treatment
  - Gabapentin 1200 mg
  - Dronabinol (synthetic cannabinoid agonist) 20 mg BID

Anesthetic Adjustment?

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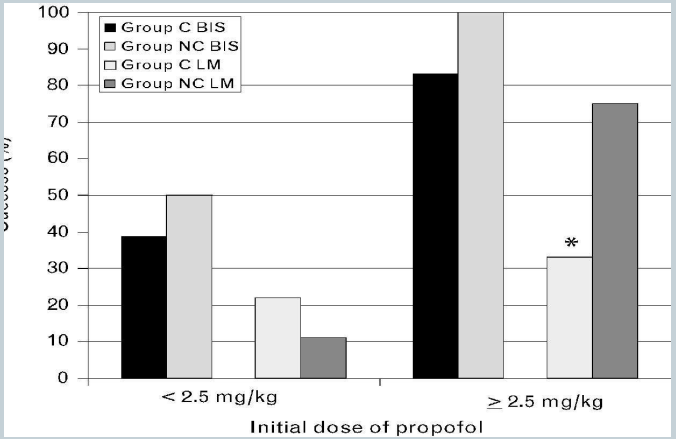
- 60 patients (>1 week usage for past 6 months)



Flisberg P et al. *Eur J Anaesthesiol*, 2009

What can we take away from this?

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1. Determine if your patient is on cannabis
   1. How do they consume it and at what frequency?
2. Do not perform elective surgery on someone who is actively intoxicated
3. Chronic cannabis users may require greater induction/maintenance doses

Questions?

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