Rollin' Into 2023: Update on Marijuana Use in Solid Organ Transplantation

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Special thank you to Jennifer Melaragno for several of these slides

Conflict of Interest

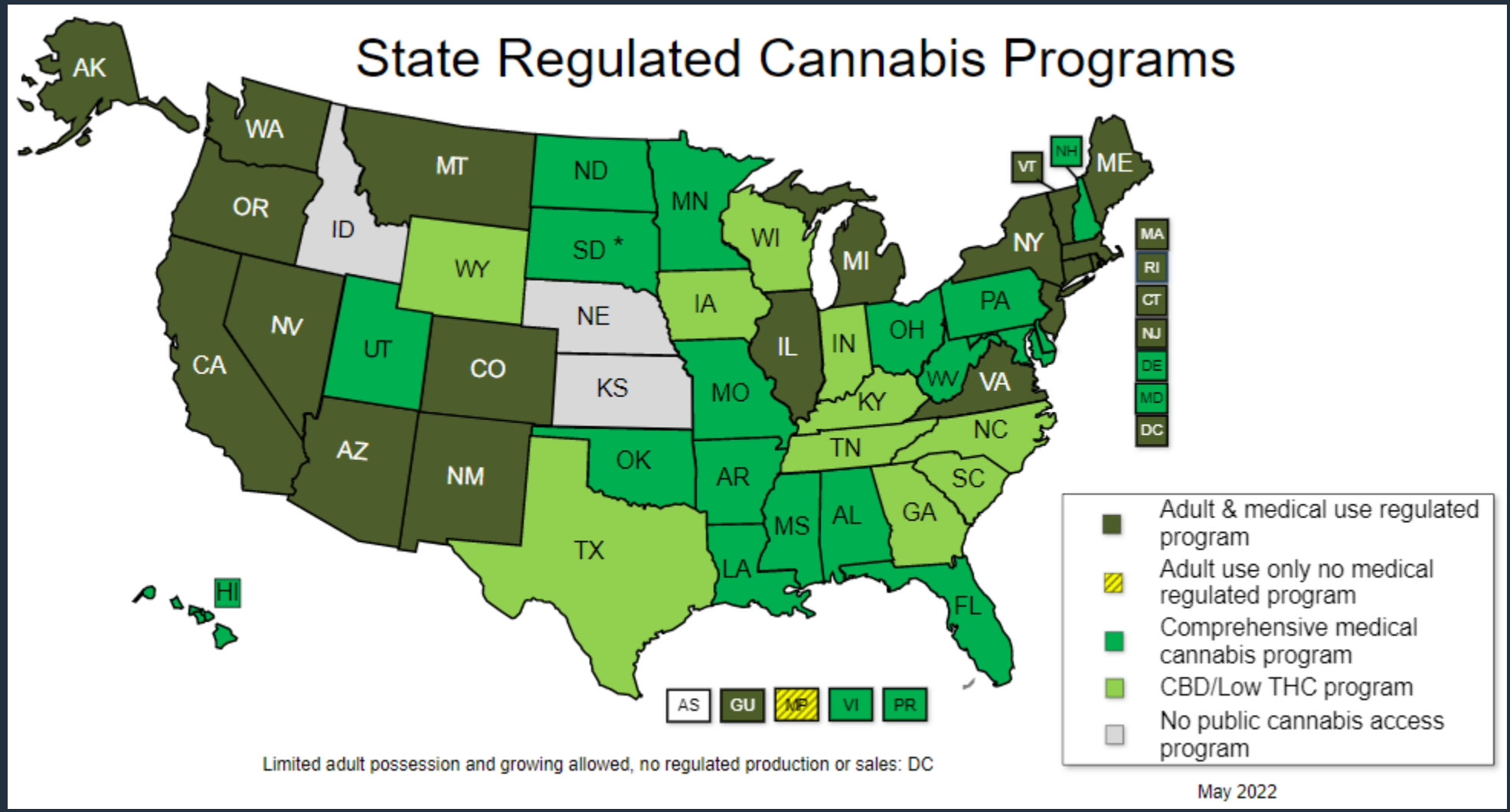
- No relevant financial discloses
- Does include discussion of off-label or investigational uses of medications

Cannabis Lingo

Cannabis	Genus of flowering plants in the family of Cannabaceae • 3 species: *Cannabis sativa, C. indica, and C. ruderalis*
Marijuana	Dried leaves, flowers, stems, and seeds from *Cannabis sativa*
Cannabinoid	Any chemical compound that acts on cannabinoid receptors
Δ^9–THC	Primary psychoactive cannabinoid of *Cannabis sativa*
Cannabidiol	Primary non-psychoactive cannabinoid of *Cannabis sativa*
Cannabinol	Mildly psychoactive cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids

PERTWEE R. BRITISH JOURNAL OF PHARMACOLOGY. 2006; 147:S163-S171.

Cannabinoid Legal Status



National Conference of State Legislatures – State Medical Marijuana Laws – Homepage. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. October 2, 2022.

Cannabis in the Medical Landscape

Dronabinol (Marinol®, Syndros®)

- Anorexia in patients with AIDS
- Chemotherapy-induced nausea and vomiting
- OSA (off-label)

Synthetic

Nabilone (Cesamet®)

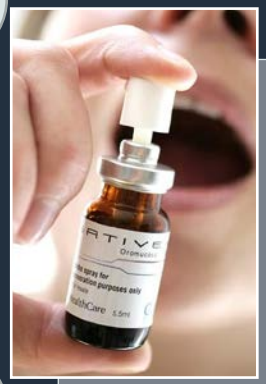
- Refractory chemotherapy induced nausea and vomiting

Synthetic

Cannabidiol (Epidiolex®)

- Seizure disorder associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥ 1 year old

CBD



Nabiximols (Sativex®) (Canada only)

- Multiple sclerosis related neuropathic pain and muscle spasticity
- Advanced cancer pain

THC
CBD

Non-FDA regulated Cannabis in the Landscape

Variable potency

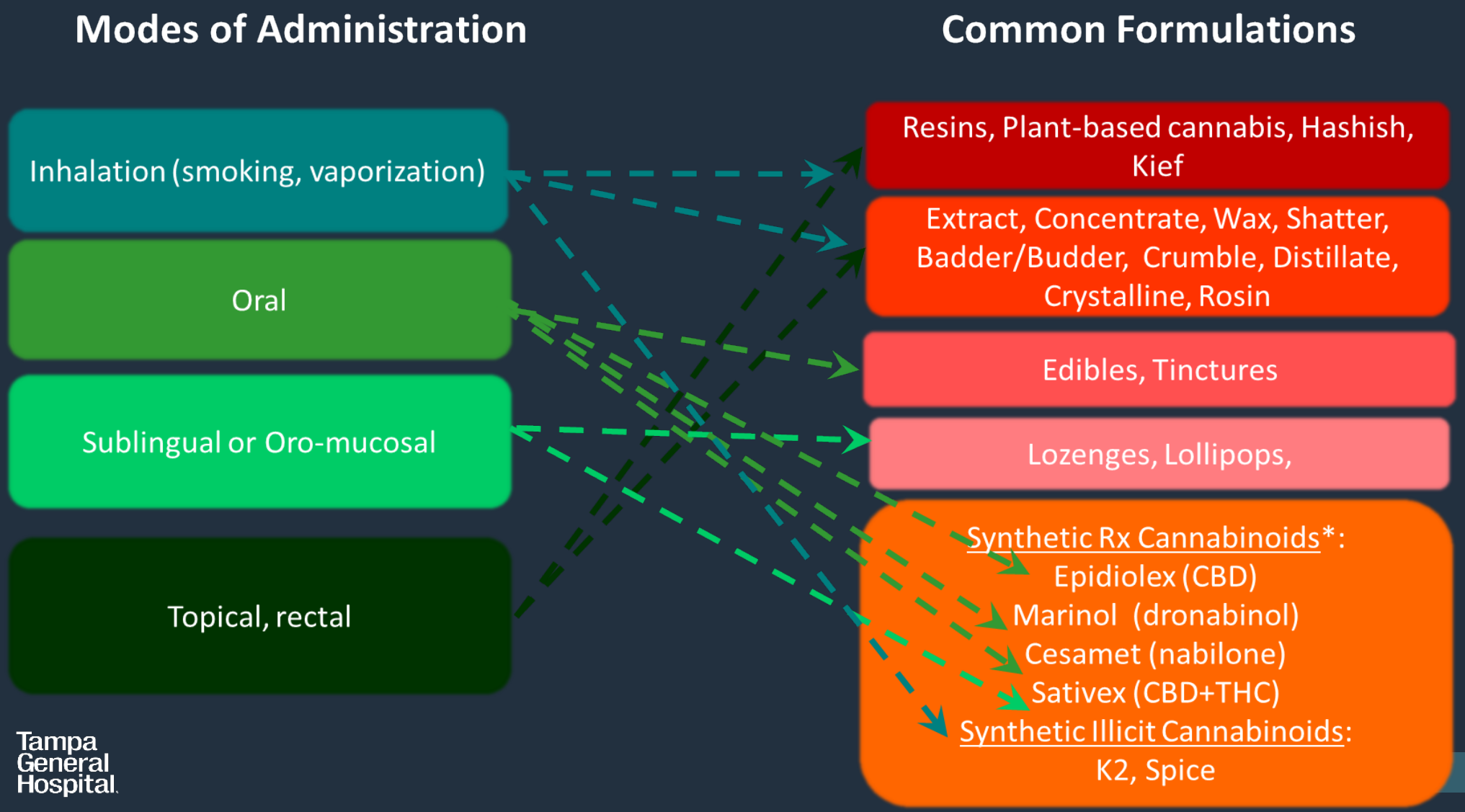
- Dependent on the species strain, cultivation and storage of the plant

Variable quality

- Microbial Contamination, Pesticides, Heavy metal accumulation (absorb via soil or added during processing)

Variable methods of administration

Product Availability



Quality: Microbial Contamination

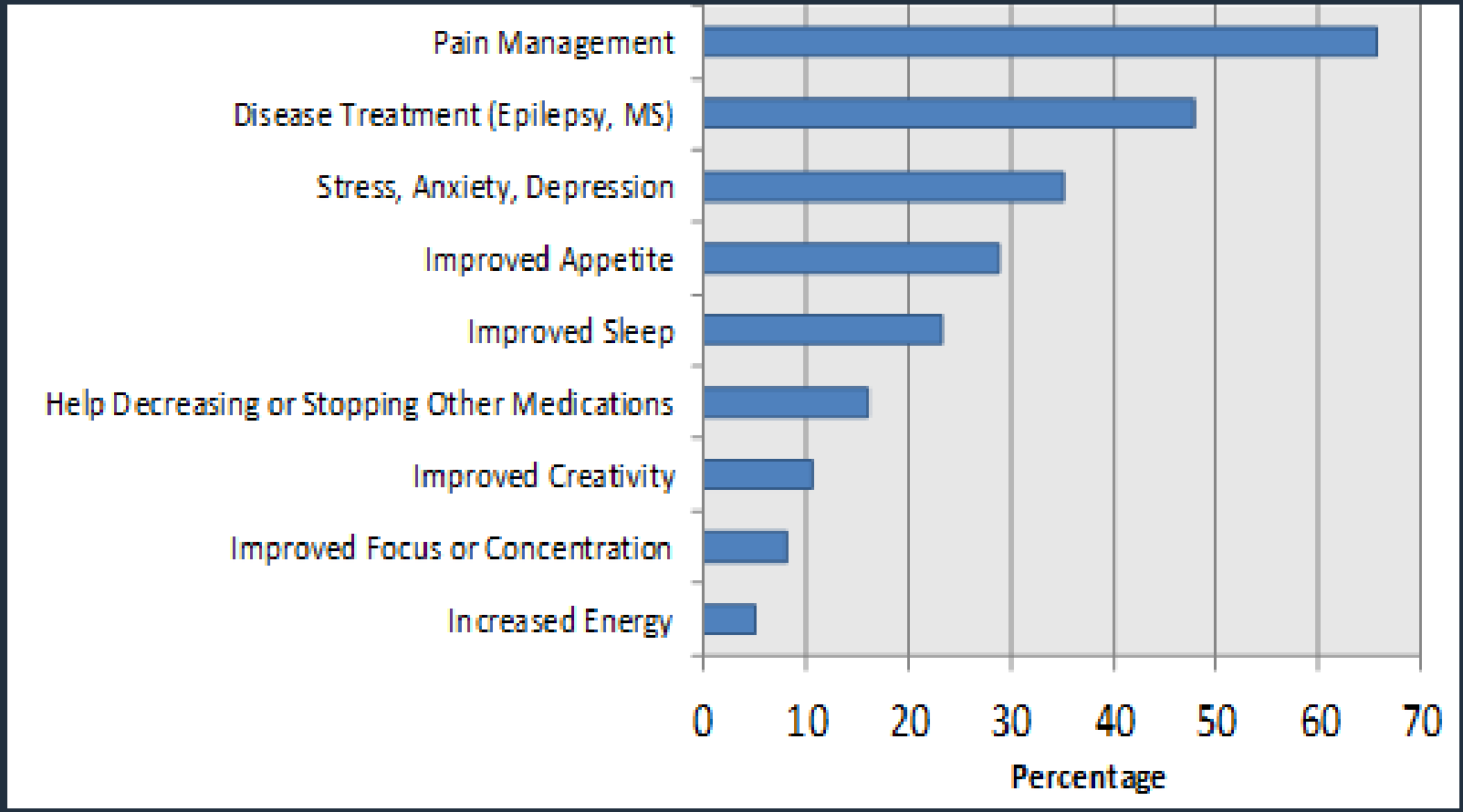
- 100 random dispensary-sourced cannabis samples from non-identical sites in the US
- All cannabis samples evaluated contained viable bacterial and fungal species that are known opportunistic pathogens
- 12% of all tested samples harbored resistance to at least one commonly prescribed antibacterial agent
- Elevated MICs were observed in all *Fusarium*, *Mucor*, and *Rhodotorula* isolates

Microorganism	% isolated
Pseudomonas spp.	60%
Pseudomonas aeruginosa	12%
Klebsiella spp	65%
Enterobacter spp.	52%
Clasdrosporium spp.	30%
Penicillium spp.	26%
Pantoea spp.	18%
Fusarium spp.	12%
Aspergillus fumigatus	12%
Rhodotorula spp.	8%
Aspergillus flavus	6%
Ledlercia spp.	5%
Cunninghamella spp.	4%
Acremonium spp.	4%
Mucor spp.	2%

McHardy I. J Infect. 2018 May;76(5):500-501.

Cannabis for Therapeutic Indication: Public Perception

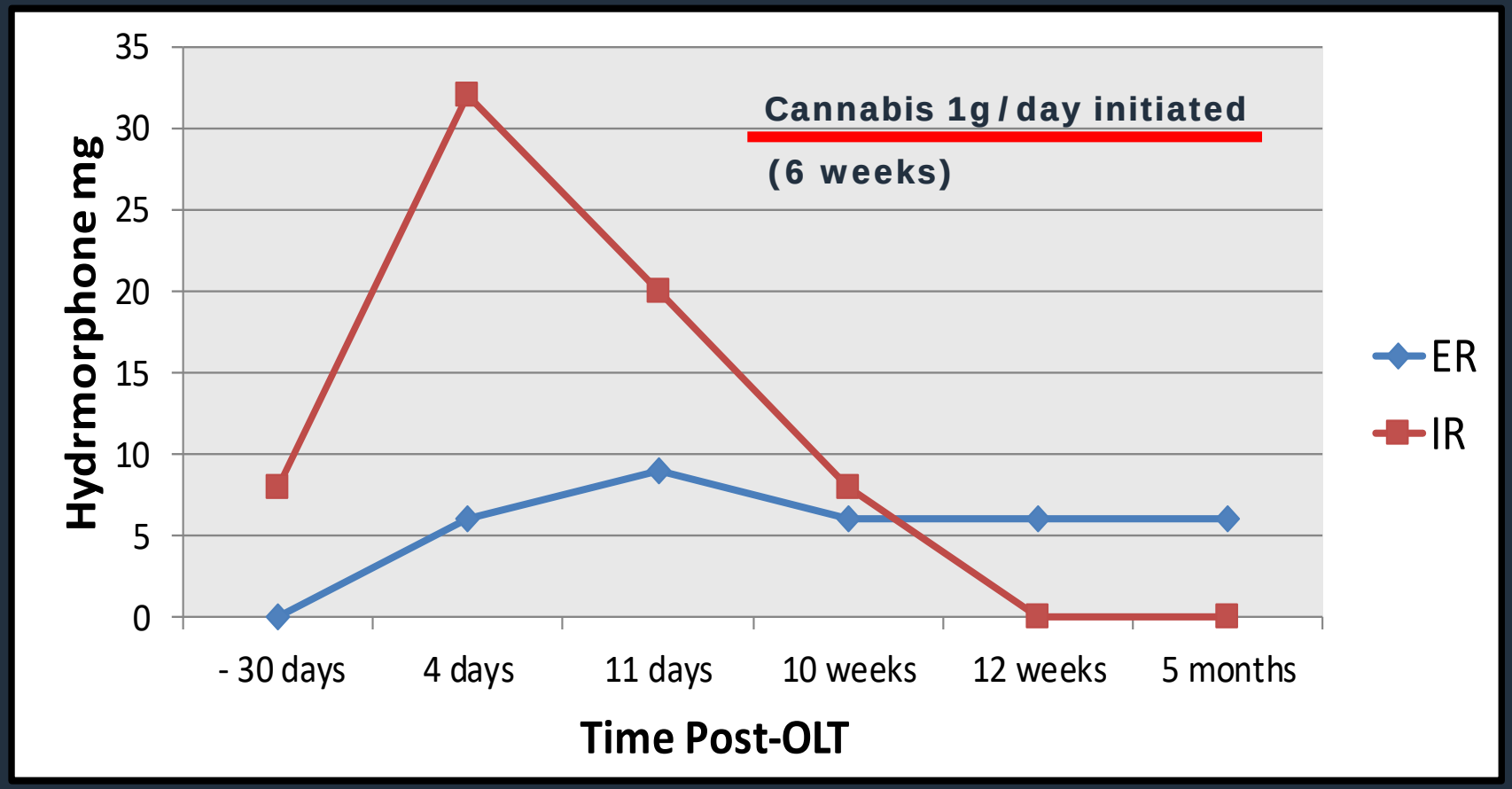
- N = 9003 adults; use in the last year: 14.6%
- Marijuana use associated with at least 1 benefit: 81%



Keyhani S. *Ann Intern Med.* 2018;169(5):282-290.

Cannabis for Therapeutic Indication:
Pain After LIVER Transplantation

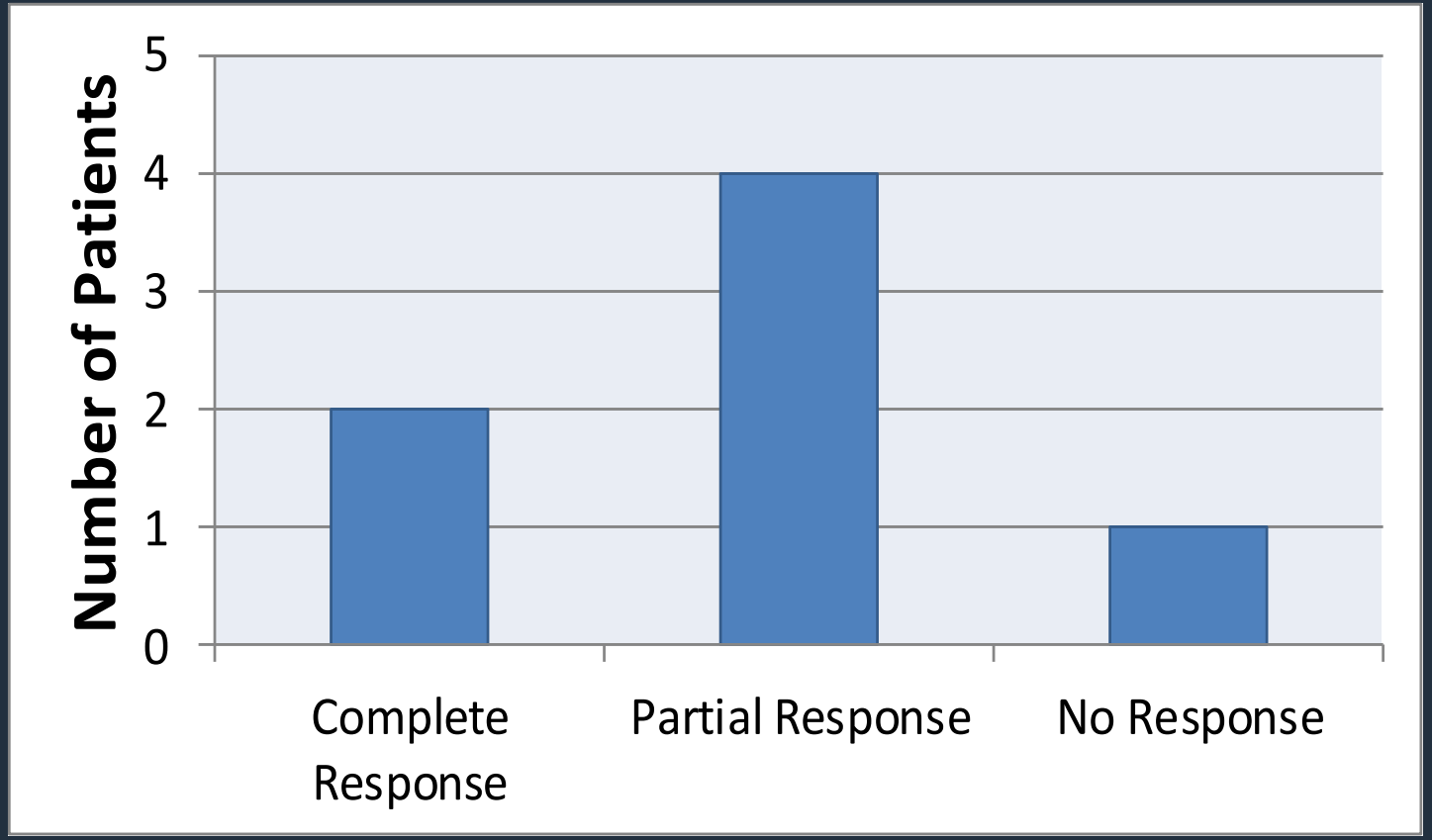
- 57 yo M with ESLD secondary to HCV & HCC
- History of chronic pain syndrome (dull - sharp abdominal pain x 4 years)



Meng H. *Canadian journal of anaesthesia.* 2016;63(3):307-310.

Cannabis for Therapeutic Indication:
PAIN After KIDNEY Transplantation

- Single center review (n= 7 patients)
- CBD 50 mg BID (up to 300 mg/day) for chronic pain management
- 2 patients required tacrolimus dosage reduction during follow-up



Cunetti L. *Transplantation proceedings.* 2018;50(2):461-464.

Pharmacokinetics & Drug Interactions

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Cannabinoid Pharmacokinetics

Parameter	Inhalation	Oral Mucosa	Gut
Bioavailability	THC: 5-7% CBD: 30%	THC: 5-7% CBD: 4%	THC: 5-7% CBD: 7-13%
Time to Cmax	1-30 min	1-4 hours	2-4 hours
Distribution	Highly lipophilic; sequesters in fatty tissues		
Duration	1-2 hours	45 min – 2 hours	5 – 8 hours
Metabolism	Hepatic; substrates of multiple CYP450 enzymes		
Elimination t ½	20 – 30 hours		

HIGH intra- & inter-patient variability

Cox EJ. Pharmacol Ther 2019;201:25-38

Drug Interactions: Δ^9-THC & CBD

- Inhibitors of CYP Enzymes
- Inducers of CYP Enzymes
- Inhibitors of P-glycoprotein
- Inhibitors of Glucuronidation
- Protein binding displacement

Drug interactions: Δ^9-THC & CBD as CYP Enzyme substrates

Δ^9-THC – Substrate of CYP3A4 and 2C9

Systemic levels of Δ^9-THC may be increased

- CYP3A4 inhibitors (e.g., ritonavir, verapamil, voriconazole)
- CYP2C9 inhibitors (e.g., fluconazole, sulfamethoxazole, voriconazole)

Systemic levels of Δ^9-THC may be reduced

- CYP3A4 inducers (e.g., carbamazepine, phenytoin, St. John's wort)
- CYP2C9 inducers (e.g., carbamazepine, phenytoin, rifampin)

CBD - Substrate of CYP3A4 and 2C19

Systemic levels of CBD may be increased

- CYP3A4 inhibitors (e.g., ritonavir, verapamil, voriconazole)
- CYP2C19 inhibitors (e.g., fluconazole, omeprazole)

Systemic levels of CBD may be reduced

- CYP3A4 inducers (e.g., carbamazepine, phenytoin, St. John's wort)
- CYP2C19 inducers (e.g., rifampin, primidone)

Drug Interactions: OLD Data

- Mice treated with CBD and CsA:
  - 60-86% ↓ in CsA metabolite formation

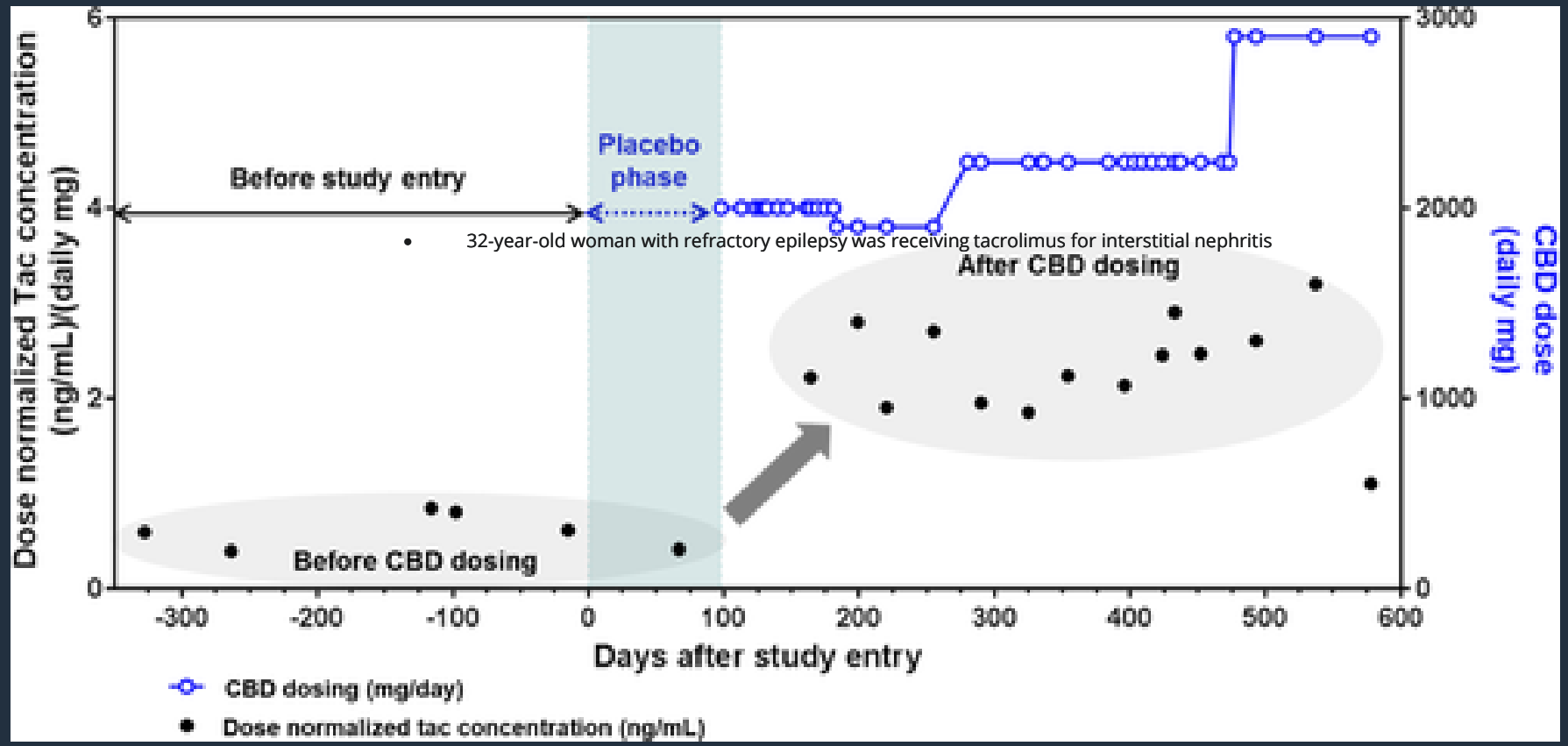
- 67yo s/p HSCT
  - Posaconazole for prophylaxis
  - Day+10, admitted use of edible marijuana gummies
  - Tacrolimus trough peak: 45.8 ng/mL; transferred to the ICU for altered mental status

- 7 KTRs using CBD for chronic pain
  - 2/7 patients required dosage reduction of tacrolimus

Yamaori S. *Life sciences.* 2011;88(15-16):730-736.
Jaeger W. *Xenobiotica.* 1996;26(3):275-284.
Hauser N. *Case reports in transplantation.* 2016;4028492.
Cunetti L. *Transplantation proceedings.* 2018;50(2):461-464.

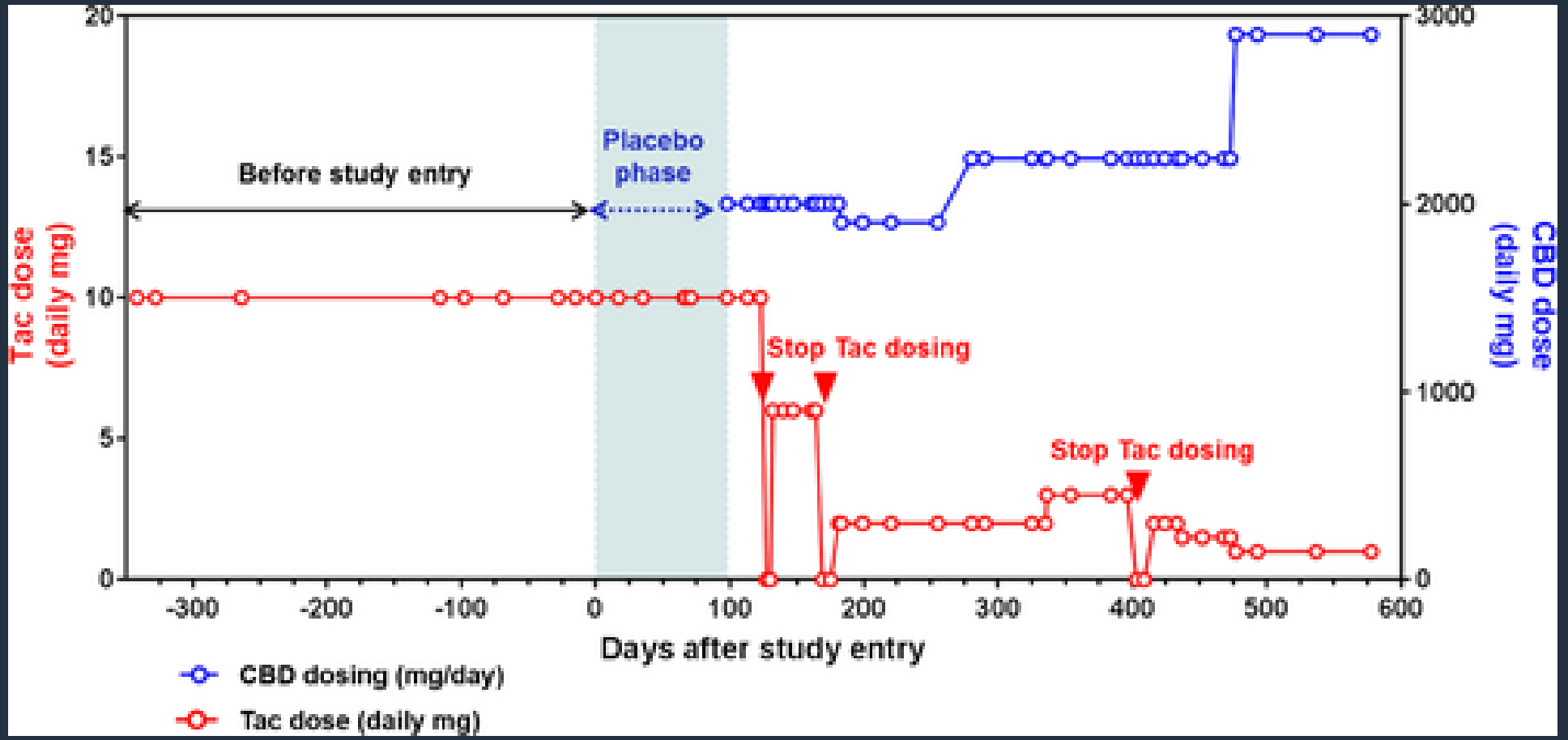
Drug-Drug Interaction: New Data

- 32-year-old woman with refractory epilepsy; tacrolimus for interstitial nephritis
- Stable tacrolimus dose (5 mg BID) prior to enrollment in CBD trial



Leino AD, et al. Am J Transplant. 2019;19:2944–2948

Drug-Drug Interaction



Leino AD, et al. Am J Transplant. 2019;19:2944–2948

Safety & Adverse Effects

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Negative Effects of Cannabis

Neuropsychiatric

- Impaired cognition
- Depression, anxiety
- Cannabis use disorder
- Withdraw syndrome
- Altered brain development (early adolescence)

Pulmonary

- Infection (*Aspergillus,* tuberculosis)
- Respiratory symptoms
- Increased episodes of chronic bronchitis

Cardiovascular

- Myocardial infarction
- Stroke (TIA, ischemic, subarachnoid)
- Cardiomyopathy, heart failure
- Arrhythmias, tachycardia

Other

- Cannabinoid hyperemesis syndrome
- Renal adverse effects?
- Cancer?

Melaragno I, et al. Transplantation 2021; 105(2):291-299.

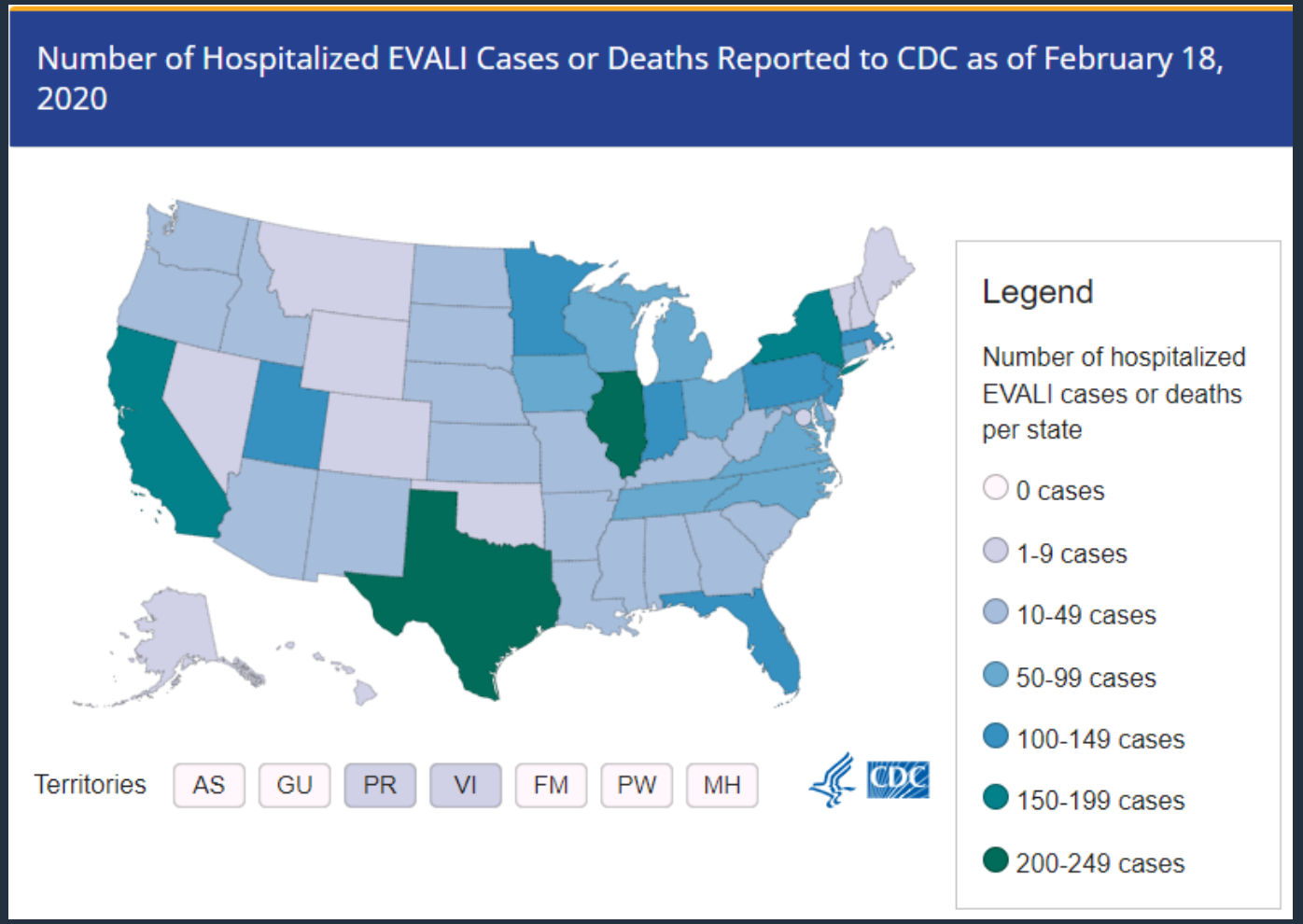
Safety & Adverse Effects:
What's OLD: Pulmonary Effects

- Cannabis smoking associated with:
  - ↑ cough, sputum production and wheeze
  - Improved airway dynamics with acute use (not chronic)
    - Bronchodilation, higher forced vital capacity
  - More frequent chronic bronchitis episodes; resolution with cessation
- Limited evidence:
  - Chronic obstructive pulmonary disease
  - Asthma

Tashkin DP. *Ann Am Thorac Soc.* 2013;10(3):239-247.
Pletcher MJ. *JAMA.* 2012;307(2):173-181.
Douglas IS. *Ann Am Thorac Soc.* 2015;12:1700-1710
Tetrault JM. Arch Intern Med 2007;167:221-228

Safety & Adverse Effects:
What's NEW: Pulmonary Effects

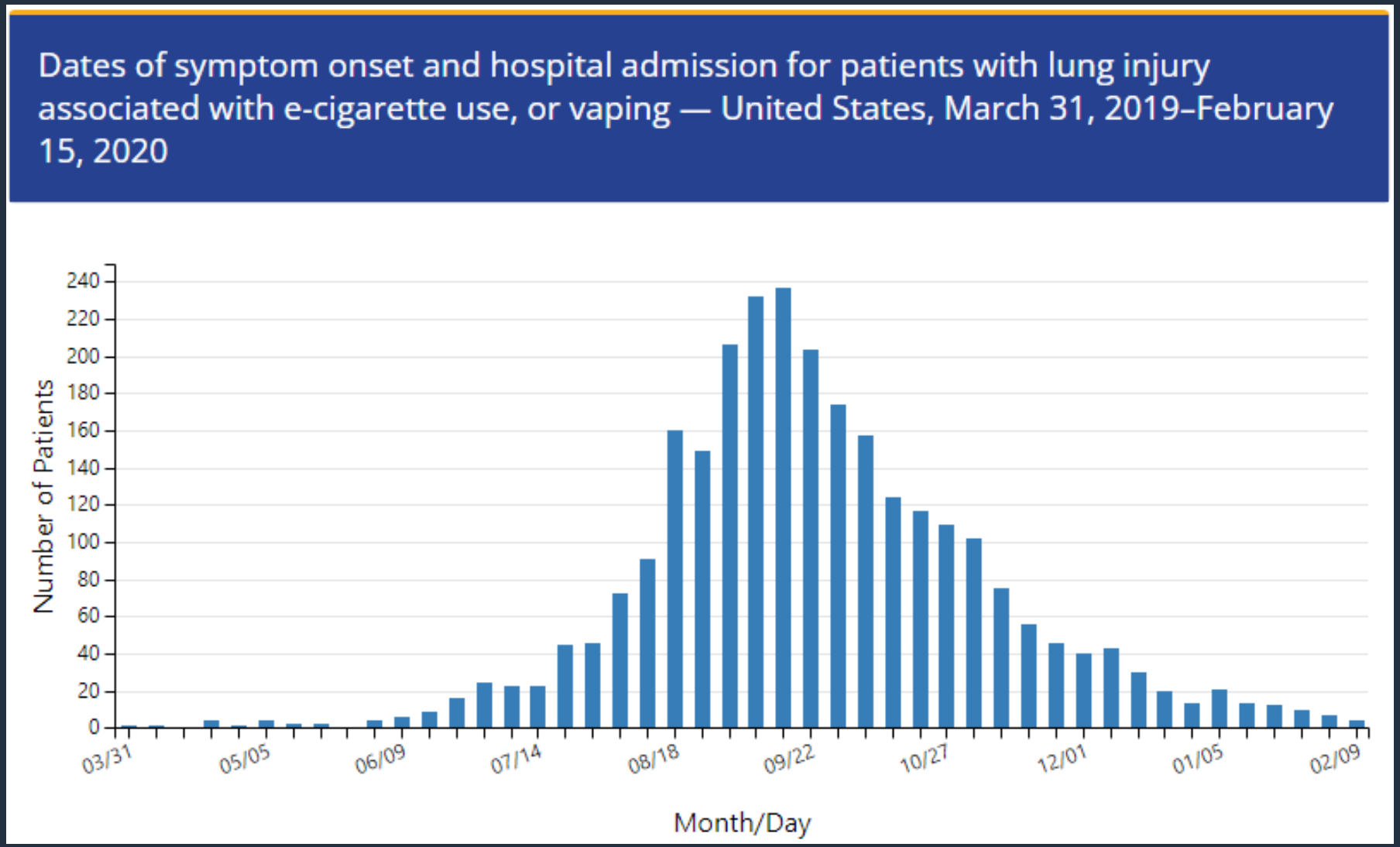
E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI)



82% reported using THC-containing products

CDC – Smoking & Tobacco Use – Homepage. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#epi-chart. October 2, 2022

EVALI Cases 2019-2020



CDC – Smoking & Tobacco Use – Homepage. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. October 2, 2022

Vitamin E Acetate Associated with EVALI

- EVALI case pts vs. healthy controls
- BAL fluid collected
- Toxicants measured
- Results (EVALI group):
  - Median age: 23 yo
  - Male: 69%
  - THC product: 77%
  - Nicotine product: 67%
- Vitamin E was associated with EVALI

Toxicant	EVALI Case Patients (n=51)	All Comparators (n=99)
Vitamin E acetate	48/51 (94)	0/99
Medium-chain triglyceride oil	0/49	0/63
Coconut oil	1/49 (2)	0/63
Plant oil	0/38	0/62
Squalane	0/38	0/98
Squalene	0/38	0/98
α-pinene	0/39	0/97
B-pinene	0/39	0/97
3-careen	0/39	0/97
Limonene	1/39 (3)	0/97
Petroleum distillates	0/12	0/98

Blount BC, et al. N Engl J Med 2020; 382:697-705

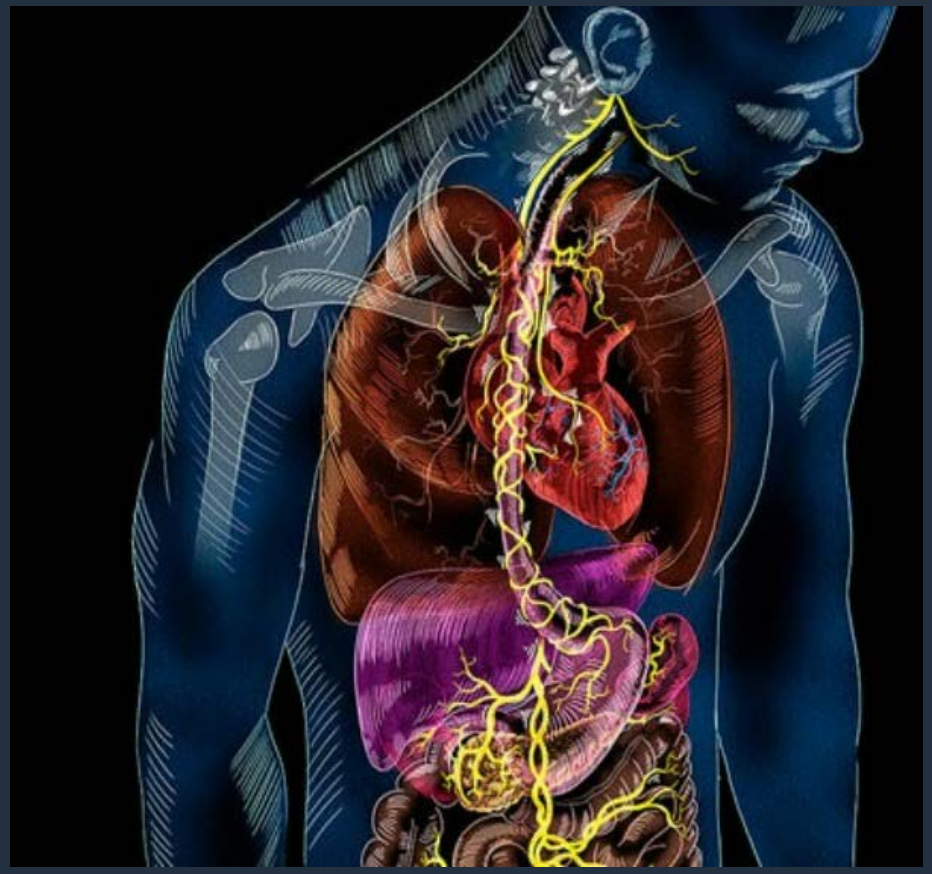
EVALI: **Recommendations from CDC & FDA**

- Do not use THC-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers
- Vitamin E acetate should not be added to any e-cigarette
- The best way to avoid potentially harmful effects is to not use THC-containing e-cigarette, or vaping, products.
- Seek treatment for cannabis use that leads to significant impairment or distress

CDC – Smoking & Tobacco Use – Homepage. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. October 2, 2022

Safety & Adverse Effects:

What's OLD but getting NEW press: Gastrointestinal



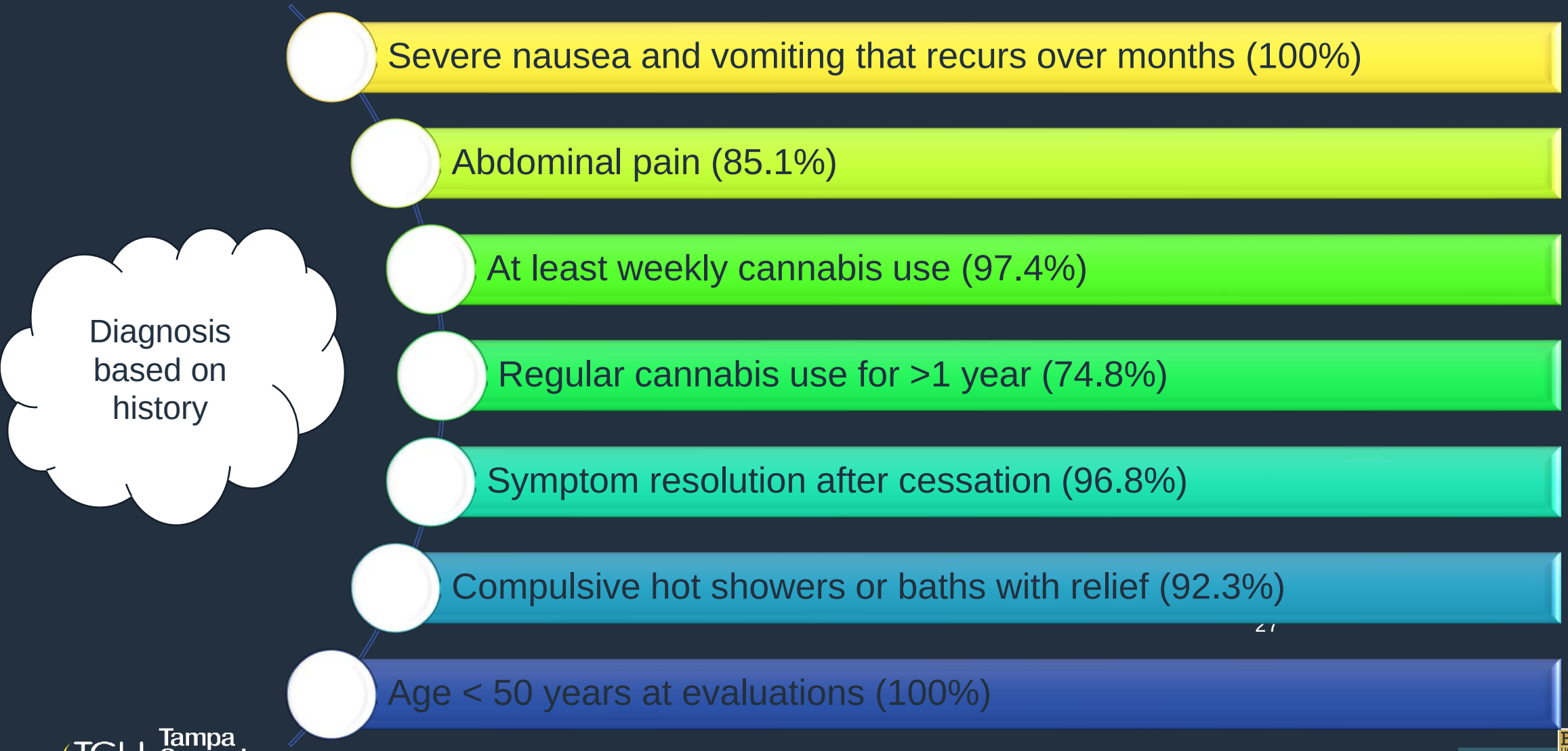
Cannabinoid Hyperemesis Syndrome

- Cyclic nausea and vomiting with abdominal pain in regular cannabis user
- Up to 6% of users

Sorenson CJ. J Med Toxicol 2017;13:71-87

Chocrin Y. BMJ 2019;366:I4336

Cannabinoid Hyperemesis Syndrome



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Sorenson CJ. J Med Toxicol 2017;13:71-87

Chocrin Y. BMJ 2019;366:l4336

Cannabinoid Hyperemesis Syndrome

- Mechanism:
  - No clear mechanism identified
  - Transient receptor potential vanilloid subtype 1 (TRPV1) receptor implicated
  - Prolonged cannabinoid exposure inactivates TRPV1 causing nausea & emesis
- Management:
  - Cannabis cessation; symptom resolution in 2 weeks
  - Supportive care (hot shower/bath)
  - Case reports:
    - Topical capsaicin
      - Produces heat sensation through activation of TRVP-1 receptors
    - Benzodiazepines, haloperidol

Sorenson CJ. J Med Toxicol 2017;13:71-87
Dezieck L. Clin Toxicol 2017;55:908
Moon AM. ACG Case Rep J. 2018; 5:e3.

Chocrin Y. BMJ 2019;366:I4336
Richards JR. Clin Toxicol 2018;56:15

Outcomes After Solid Organ Transplant

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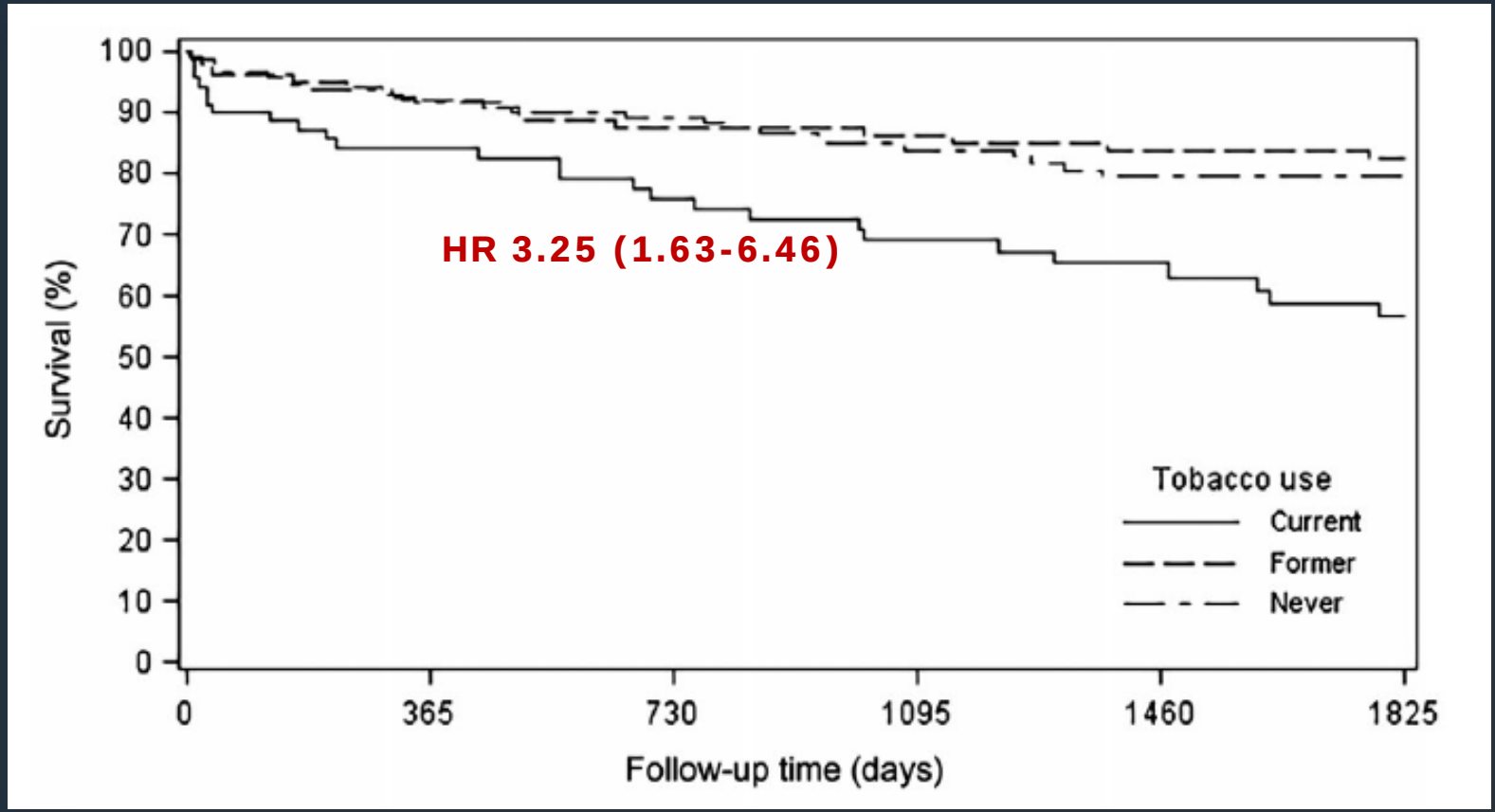
Effect of Cannabis on Outcomes After Liver Transplant

- Single center, retrospective review (n = 316)
- 54% tobacco smokers, 26% marijuana smokers, 20% both



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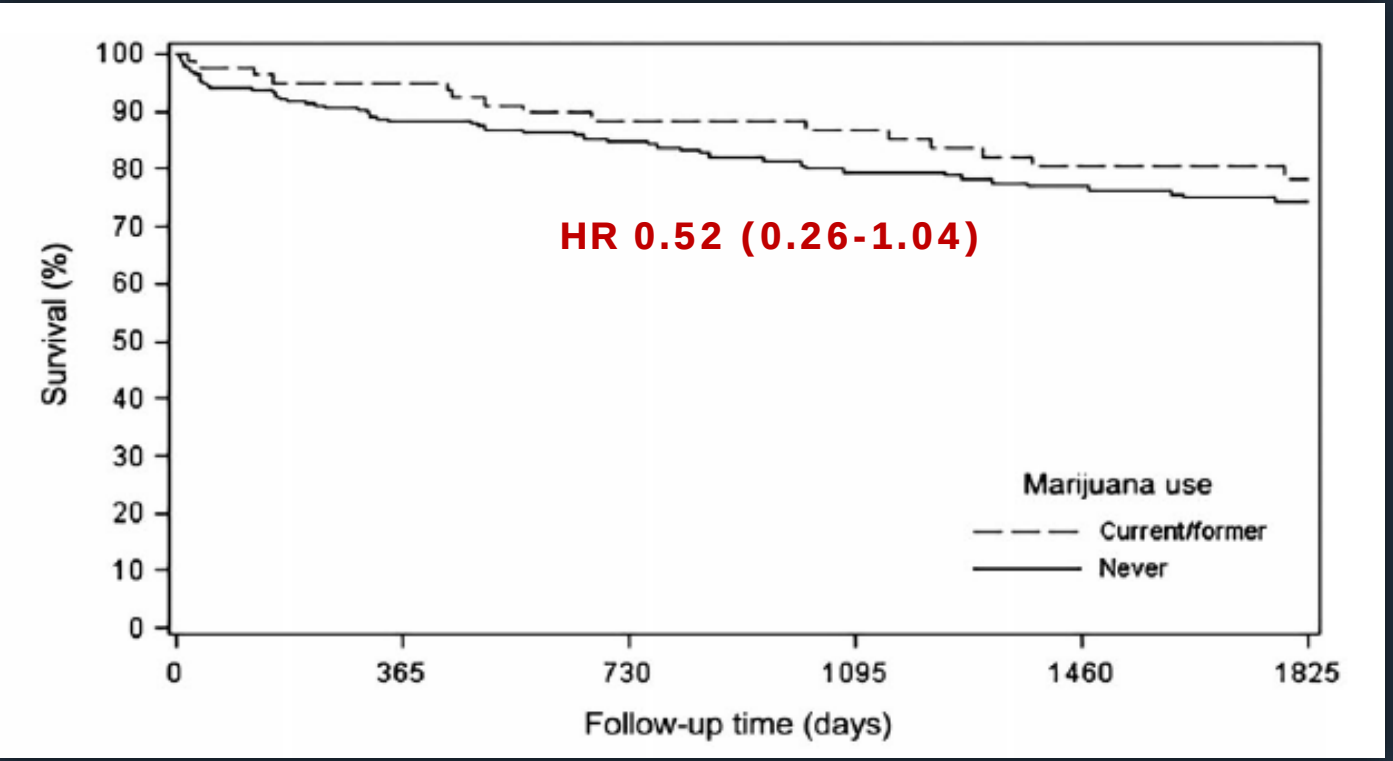
Adapted from “Marijuana Consumption in Liver Transplant Patients,” by PS. Rodriguez, PD. Strassle, AS. Barritt, et al, 2019, *Liver Transplantation, 25, 734*. Copyright 2019 “American Association for the Study of Liver Diseases". Adapted with permission.

Effect of Cannabis on Outcomes After Liver Transplant



Pretransplant marijuana use, past or current, does not appear to impact liver transplant outcomes [31]

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Adapted from “Marijuana Consumption in Liver Transplant Patients,” by PS. Rodriguez, PD. Strassle, AS. Barritt, et al, 2019, *Liver Transplantation, 25, 734*. Copyright 2019 “American Association for the Study of Liver Diseases". Adapted with permission.

Effect of Cannabis on Outcomes After Kidney Transplant

- Single center retrospective review (n=1225)
- Marijuana use was not associated with worse outcomes
  - Adjusted OR 0.79 (95% CI 0.28–2.28, *p*=0.67)

	MJ non-users (n = 1169)	MJ users (n=56)	p-value
Patient survival (%)	97.7	100	0.62
Graft failure[a] (%)	17.4	19.7	0.62
Mean creatinine of functioning grafts, mg/dL	1.42 (1.42 – 1.49)	1.52 (1.39 – 1.69)	0.38
Mean GFR of functioning grafts, mL/min^2	49.5 (48.3 – 50.7)	50.7 (45.6 – 56.5)	0.65

[a]Defined as GFR < 20 mL/min/1.73m2 at 1 year

Greenan G. *Clinical transplantation.* 2016;30(10):1340-1346.

Safety & Adverse Effects: Neuropsychiatric

Effects in the general population:

- Impaired decision making, planning, impulse control, cognition, memory

- *Acute problems:*
  - Intoxication, withdrawal, intoxication delirium, psychotic disorder, anxiety disorder, sleep disorder

- *Chronic problem:*
  - Cannabis use disorder

33

Sachs J. *Neurotherapeutics* . 2015;12(4):735-746.
Tait RJ. *Clinical toxicology (Philadelphia, Pa.).* 2016;54(1):1-13.
Marconi A. *Schizophrenia bulletin.* 2016;42(5):1262-1269.

Cannabis Use Disorder (CUD)

Problematic pattern of cannabis use leading to clinically significant impairment or distress as manifested by at least 2 of the following, occurring within a 12-month period:
Cannabis is often taken in larger amounts over a longer period than intended
Persistent desire or unsuccessful efforts to cut down or control use
A great deal of time spent in activities necessary to obtain or use cannabis or recovering from its effects
Craving, strong desire, or urge to use cannabis
Failure to fulfill role obligations at home, school, or work due to recurrent cannabis use
Ongoing cannabis use despite persistent/recurrent social or interpersonal problems caused/exacerbated by effects of cannabis
Important social, occupational, or recreational activities are given up or reduced because of cannabis use
Recurrent cannabis use in situations in which it is physically hazardous
Continuing cannabis use despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis
Tolerance, defined by either: (1) a need for markedly increased cannabis to achieve intoxication or desired effect, or (2) a markedly diminished effect with continued use of the same amount of the substance
Withdrawal, manifested by either characteristic withdrawal syndrome or cannabis is taken to relieve/avoid withdrawal symptoms.

American Psychiatric Association. DSM5. Washington, DC, 2013 Hasin DS. Am J Psychiatry. 2016;173(6):588-599
Hasin DS. JAMA Psychiatry. 2015;72(12):1235

Effect of Cannabis on Outcomes After Kidney Transplant

- SRTR Database study (2007-2015)
- 52,689 KTRs
- Cannabis dependence or abuse (CDOA): 1yr pre-KTR: 0.5%; 1yr post-KTR: 0.3%

CDOA year before transplant		
	aHR	95% CI
Death-censored graft failure:	1.00	0.54-1.87
All-cause graft loss:	1.10	0.67-1.80
Death:	1.09	0.49-2.44
CDOA first year post-transplant		
Death-censored graft failure:	2.29	1.59-3.32
All-cause graft loss:	2.09	1.50-2.91
Death:	1.79	1.06-3.04

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Alhamad T. Transplantation. 2019;103(11):2373

Cannabis Users as Donors

- Single center retrospective review (n = 294 patients)
- Living kidney donors; January 2000 – May 2016
- Outcomes compared based on marijuana use

		Donors			Recipients		
	Time (months)	MUD (n=31)	NMUD (n=263)	P value	MKR (n=27)	NMKR (n=203)	P value
Mean creatinine change (mg/dL)	1	0.381	0.456	0.051	-0.022	-0.195	0.089
	6	0.313	0.378	0.493	0.084	-0.087	0.284
	12	0.367	0.339	0.694	0.041	-0.105	0.427
Mean eGFR change (mL/min/1.73m²)	1	-36.5	-41.8	0.112	-4.91	3.43	0.010
	6	-31.9	-36.2	0.640	-8.76	-3.88	0.357
	12	-36.3	-32.4	0.559	-5.01	-4.12	0.879

Ruckle D Clin Kidney J 2018;12(3):437-442.

Patient Case: Cannabis Withdrawal

The patient 29-year-old male with a history of kidney transplant in 2020 presents to emergency department following a syncopal spell, trouble sleeping, chest pain, diaphoresis, nausea and shortness of breath.

Patient “denies” alcohol, tobacco, or drug use.

Medications:

1. Tacrolimus 5mg BID
2. MMF 500mg BID
3. Prednisone 5mg daily
4. Amlodipine 5mg daily

Cannabis Withdrawal Symptoms

- Insomnia, night sweats, nightmares, vivid dreams
- Depression, anxiety, anger, fear
- Headaches
- Tremors, shaking, dizziness
- Loss of appetite, digestion issues

Cannabis Withdrawal: Treatment Considerations

- Very limited data (no head-to-head trials)
- Treat acute symptoms
- Moderate/Severe symptoms: dronabinol, gabapentin
- Consider SSRI to reduce anxiety/withdrawal symptoms

Sherman BJ. Pharmacotherapy 2016; 36(5): 511-535.

Implementing a Cannabis Policy: Key Considerations

1. Develop a policy/stance!
   - 31% of programs surveyed would describe their policy as “don’t ask, don’t tell”
2. Pre-transplant
   - Assessment of substance use disorder as part of psychosocial evaluation for all SOT candidates
   - Abstain from recreational use (medical use should be prescribed legally and only ingested or used topically)
3. Post-transplant
   - Initiation of cannabis should be deferred until a period of graft stability has been achieved
   - Counsel patients on risks (interaction with immunosuppression, unknown effects on allograft, other risks)
   - NO smoking or vaping!
   - Treat as a prescription medications (consistent product and consistent use, purchased from licensed distributor)
   - Therapeutic drug monitoring of immunosuppressants cannabis initiation (eg, weekly X1 month then monthly)

Conclusion

- Cannabis use in increasing
- Establish and maintain a nonjudgmental and open atmosphere in discussions surrounding cannabis pre- and post-transplant
- Clinicians should be knowledgeable of potential risks and able to educate patients on risks
- A cannabis policy/stance is imperative


Questions?