Marijuana, Hemp, and the Child with Cancer

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Disclosures

- I have no industry relationships to disclose.
- I will be talking about off-label use of medications.

Time for Voting

Participant Poll

A. Do you know the state laws regarding medical and recreational marijuana where you practice?

1. Yes
2. Somewhat
3. No

Participant Poll

B. Does your practice site have a policy or protocol regarding marijuana use by patients at your institution?

1. Yes
2. No
3. Don't know

Participant Poll

C. Are you comfortable asking the families you care for about their use of marijuana?

1. Yes
2. Somewhat
3. No

Participant Poll

D. Are you comfortable giving information about marijuana use to the children and families you care for?

1. Yes
2. Somewhat
3. No

Participant Poll

E. Do you know a resource to find more information about marijuana?

1. Yes
2. Somewhat
3. No

Objectives

- Learn about the basics of cannabis
- State and federal current laws
- Studies of marijuana in pediatric cancer
- Initial findings of a prospective observational study of medical marijuana on the quality of life and immune function of brain tumor patients
- Pharmacological interactions with CBD and THC
- Nurses role in facilitating discussions and protocols

Primer on Cannabis

- Hemp and marijuana are both one species: *Cannabis sativa*
- **Marijuana** is any cannabis plant with more than 0.3 percent THC
- **Hemp** cannot legally contain more than 0.3 percent THC
- Almost no restrictions on the hundreds of other compounds made by the plant, such as terpenes
- Always a hang up! Marijuana and hemp produce CBD. If your purified CBD comes from hemp plants, it is federally legal, but if it comes from a marijuana plant, **it is illegal**. That's because marijuana plants themselves **are prohibited by the DEA**.

CBD versus THC

- Both THC and CBD are members of a chemical family called cannabinoids
- Cannabinoids are plants oils, and cannabis comes packed with more than 100!

https://kuribl.com/cbd-vs-thc/

CBD versus THC: Conditions Treated

CBD	THC
Pediatric Epilepsy	Pain
Anxiety	Anxiety (less evidence)
Insomnia	Insomnia
Inflammatory and Neuropathic Pain	Muscle Spasticity
Migraines	Poor Appetite/Nausea

CBD versus THC: Side Effects

CBD	THC
Nausea	Memory Loss
Fatigue	Anxiety
Irritability	Increased HR, dry mouth, red eyes
Drowsiness	Coordination Problems
Drug Interactions	Slower Reaction Time

One More Distinction

- **Indicas:** relaxing body high, help with pain, anxiety or insomnia. Typically contain higher levels of CBD

- **Sativas:** often used by recreational consumer due to higher levels of THC giving a more uplifting and energetic high. It can cause problems for those who experience marijuana-induced paranoid or anxiety.

- **Hybrids:** hybrid cannabis strains are made by crossing the genotypes of two different strains through self-pollination. The resulting strain might land anywhere on the Indica/Sativa spectrum, depending on the characteristics of the final phenotype.

Dosage Forms

Best
- Tincture, oil, salve, patch

Mmmm. Ok
- Wax, edibles

Nope
- Flower, hash, vape pens, shatter

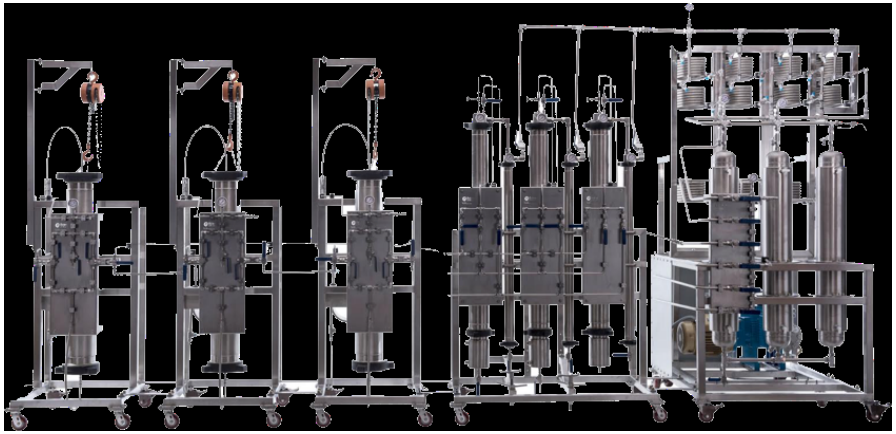
Marijuana Extraction Methods

- **Butane**: The cannabis and liquid butane are put in a pressurized and heated system. By using evaporation under a vacuum, it is then possible to remove the butane solvent. Must be tested to ensure no residual butane is present.
  - Benefit: Low cost and the higher terpene content makes it more flavorful

- **Alcohol**: The cannabis soaks in alcohol, usually ethanol, the plant material is then removed, the liquid filtered, and the alcohol is removed with some form of evaporation.
  - Benefit: no risk of leaving toxic residual chemicals in the final cannabis extract and enables the co-extraction of cannabinoids and terpenoids

Marijuana Extraction Methods

- **CO2**: Removes cannabis components from the plant matrix with carbon dioxide. High pressure and heat are used to turn the CO2 simultaneously into a liquid and a gas. The CO2 is then run through a condenser so it can be used multiple times.
  - Benefit: produces higher yields with less valuable material lost. Method can be adjusted to extract specific compounds by changing the temperature, pressure or run time. If any CO2 remains in an extract after the process it just evaporates. That is especially important for any preparations for medical uses as a producer using this method can guarantee that absolutely no residual solvent will be present in the final product.

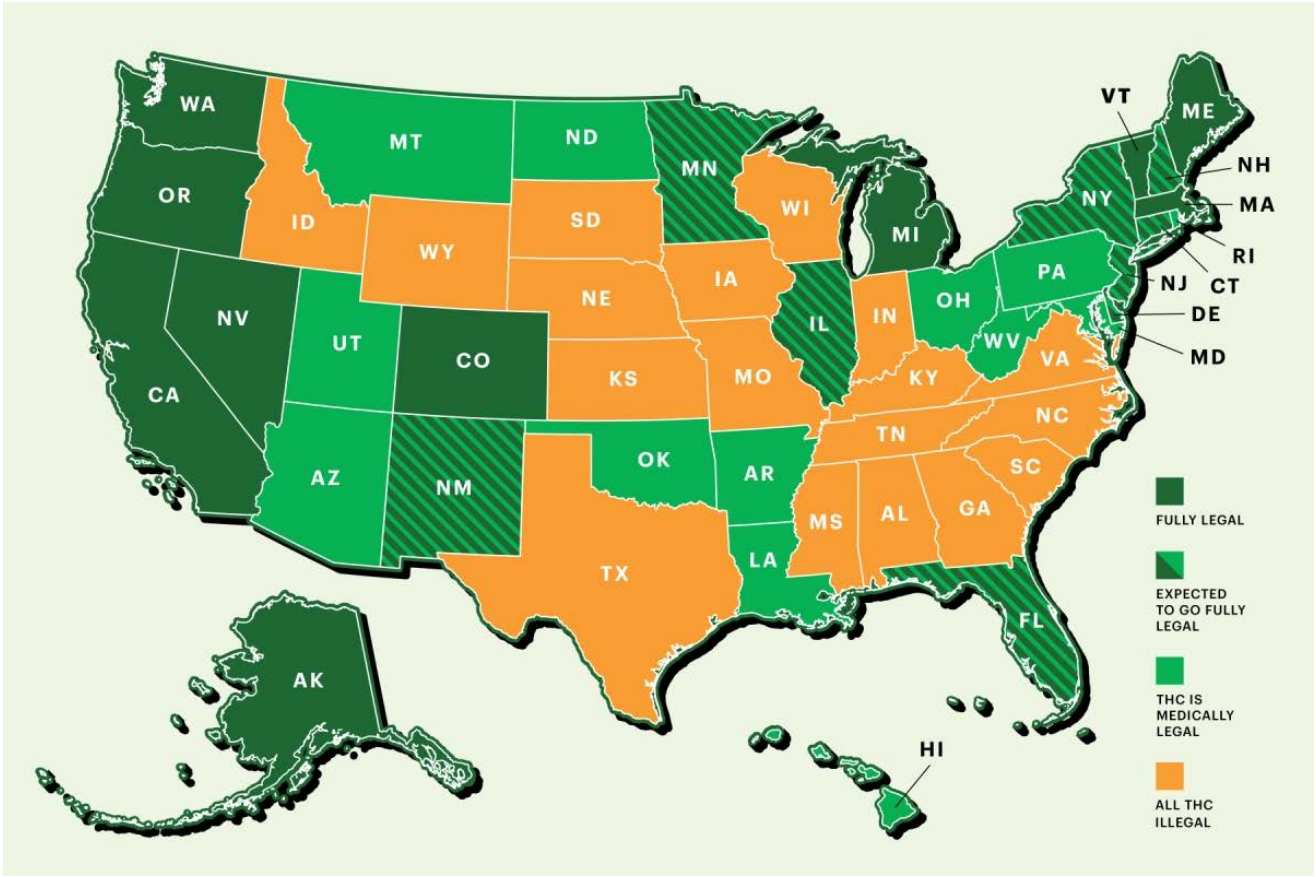


https://www.analyticalcannabis.com/articles/the-best-cannabis-extraction-methods-for-marijuana-concentrates-300434

State of the Marijuana Union

- State Legalization
  - 11 states and DC have both recreational and medical use in adults greater than 21 years old
  - Illinois is the most recent state to legalize marijuana
  - 33 states have legalized medical marijuana

- 2018 Farm Bill
  - Legalized the production of hemp as an agricultural commodity
  - Removed it from the list of controlled substances
  - Industrial hemp is defined as Cannabis sativa L. and required to be below a THC threshold of 0.3%
  - Still not legal to grow hemp in Idaho, Mississippi, New Hampshire and South Dakota
  - Federally legal to purchase hemp based CBD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FULLY LEGAL
EXPECTED TO GO FULLY LEGAL
THC IS MEDICALLY LEGAL
ALL THC ILLEGAL

Research Review

- Anecdotal reports in the lay literature describe cures of terminal brain tumors with cannabinoids alone
- Documentary “Run From the Cure: The Rick Simpson Story” about Rick Simpson Oil (RSO)
- Recent preclinical data of effect of cannabinoids in xenograft models of glioblastoma received publicity in lay press[1]

[1]Scott K, et al The Combination of Cannabidiol and Δ9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model. Mol Cancer Ther 2014; 13(12*); 2955–67.*

Discovery of high concentrations of cannabinoid receptors on certain pediatric CNS tumor cells[1]

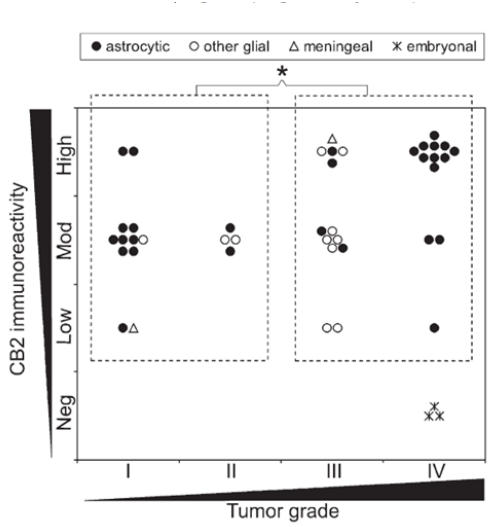
Present primarily on astrocytic tumors

Low to absent on embryonal tumors

Table 1 – Expression level of cannabinoid receptor type 2 (CB2) evaluated in adult and pediatric brain tumors

Tumor	Immunoreactivity score (CB2)	Tumor grade			
		I	II	III	IV
Adult ($n=20$)	Negative	–	–	–	–
	Low	–	–	2[a]	1
	Moderate	2[b]	2[c]	3[d]	2
	High	–	–	1	7
Pediatric ($n=25$)	Negative	–	–	–	3[e]
	Low	2[f]	–	–	–
	Moderate	6	2[g]	3[h]	–
	High	2	–	4[i]	3

All cases were classified into groups according to diagnosed WHO grade, regardless of the histopathological type of tumor. Numbers of cases refer to astrocytic tumors, which were the most abundant, and where indicated also include: [a]anaplastic oligodendroglioma ($n=2$); [b]ganglioglioma ($n=1$); [c]oligodendroglioma ($n=1$) [d]anaplastic ependymoma ($n=1$); [e]medulloblastoma ($n=2$) and S-PNET ($n=1$); [f]fibroblastic meningioma ($n=1$); [g]astrooligodendroglioma ($n=1$) and ependymoma ($n=1$); [h]anaplastic ependymoma ($n=2$) and anaplastic ganglioglioma ($n=1$); [i]anaplastic meningioma ($n=1$), anaplastic ganglioglioma ($n=1$) and anaplastic ependymoma ($n=1$). Immunoreactivity was scored as negative, low, moderate or high, depending on the intensity of DAB staining.



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[1]Ellert-Miklaszewska A, et al. Distinctive pattern of cannabinoid receptor type II (CB2) expression in adult and pediatric brain tumors. Brain Res 2007;1137(1):161-169

Preclinical studies have investigated the effects of cannabinoids on gliomas[1]

- Variable mechanisms postulated for potential anti-tumor effects
  - Inhibition of angiogenesis
  - Modulation of autophagy
  - Induction of apoptosis
  - Inhibition of tumor migration/metastasis

Little published clinical evidence exists to support the antitumor effects of cannabinoids on CNS tumors

- One published clinical trial of adults with recurrent glioblastoma (GBM) treated with THC
  - n=9 adults with recurrent GBM after standard therapy were treated with repeat surgical resection and instillation of THC into the site of the surgical resection.[2]
  - Median survival time was 24 weeks (range, 9-53 weeks)
  - Due to the small sample size, no statistically significant effect on PFS

[1]Rocha FCM, et al. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. J Neurooncol 2014;116(1):11-24
[2]Guzman M, et al. A pilot clinical study of A9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Brit J Cancer 2006; 95:197-203.

Effect of cannabinoids in management of cancer-related symptoms, including **nausea**, **anorexia**, and **pain**, has been evaluated for ~4 decades

- Nausea control
  - Clinical trials in adults and children have compared the effectiveness of THC versus placebo or other antiemetic medications
    - Cannabinoids have been shown to be more effective than placebo, metoclopramide, and prochlorperazine for nausea[1-2]
  - Major clinical oncology organizations do not recommend cannabinoids as first-line management of CINV
    - Dronabinol is FDA-approved for chemotherapy-induced nausea and vomiting (CINV) in adults who have failed conventional antiemetics

[1]Sallan SE, Zinberg NE, Frei E 3rd. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med. 1975;293(16):795-7.
[2]Phillips RS, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database of Systemic Reviews 2016; 2:1-24.

Effect of cannabinoids in management of cancer-related symptoms, including **nausea**, **anorexia**, and **pain**, has been evaluated for ~4 decades

- Appetite stimulation
  - Dronabinol is FDA-approved for wasting associated with AIDS
  - Cannabinoids have not demonstrated appetite stimulation to date in cancer-related anorexia-cachexia in adults[1]
    - In adults with cancer, dronabinol has inferior effect as compared to megestrol on anorexia[2]
- Pain control
  - Animal studies have suggested that cannabinoids act through mechanisms distinct from opioids and may have additive analgesic effects
  - Effects in humans have been evaluated through several clinical trials
    - Meta-analysis of available studies demonstrated that average number of patients who reported pain reduction by cannabinoids is larger than those treated with placebo (OR, 1.41 [95% CI, 0.99-2.00] (n=8 trials)[3]

[1]Strasser F, et al. Comparison of Orally Administered Cannabis Extract and Delt-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome. J Clin Oncol 2006;24(21):3394-3400
[2]Jatoi A, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol 2002;20(2):567-73.
[3]Whiting P, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA. 2015;313(24):2456-2473

Children's Hospital Colorado Study

- Use of Cannabinoids in the Pediatric Central Nervous System Tumor Population
  - Kathleen Dorris, Jessica Channell, Ashley Mettetal, Molly Hemenway, Angelina Baroffio, Michael Ellison, Natalie Brionse, Andrea Griesinger, Andrew Donson, Rajeev Vibhakar, Adam Green, Anandani Nellan, Jean Mulcahy Levy, Daniel Ambruso, and Nicholas Foreman
  - Will be presented at the International Society of Pediatric Neuro-Oncology at the conference in Japan in December 2020

Children's Hospital Colorado Study

- A prospective observational study has been ongoing since 2016 at Children's Hospital Colorado to evaluate cannabinoids' impact on quality of life
- Patients with CNS tumors who are 2-18 years old and used cannabinoid products
- Used PedsQL™ modules on quality of life (parent and child modules)
- Laboratory assessments of T-cell activity and pharmacokinetics of CBD, THC and associated metabolites are in process
- Diaries collected exploratory information on cannabinoid use patterns and whether it decreased use of other pharmaceuticals

Children's Hospital Colorado Study

- Thirty-three patients (14:19; male:female) have been enrolled with a median age of 6.4 years (range, 2.9-17.7 years)
- The most common tumor type in enrolled patients was embryonal tumors (13/33; 39%); nine (27%) patients had low-grade glial/glioneuronal tumors and eight (24%) had high-grade/diffuse midline gliomas. The remaining patients had ependymoma or craniopharyngioma.
- The median time on cannabinoids was 9 months
- Most (n=20) patients used oral products with both CBD and THC
- Preliminary immune function analyses identified impaired neutrophil superoxide anion production and chemotaxis in patients taking cannabinoids at early time points on therapy.
- CONCLUSIONS: Families of children with various CNS tumors are pursuing cannabinoid therapy for both antitumor and supportive care purposes. Analysis of the impact of cannabinoid use on patients' quality of life is ongoing.

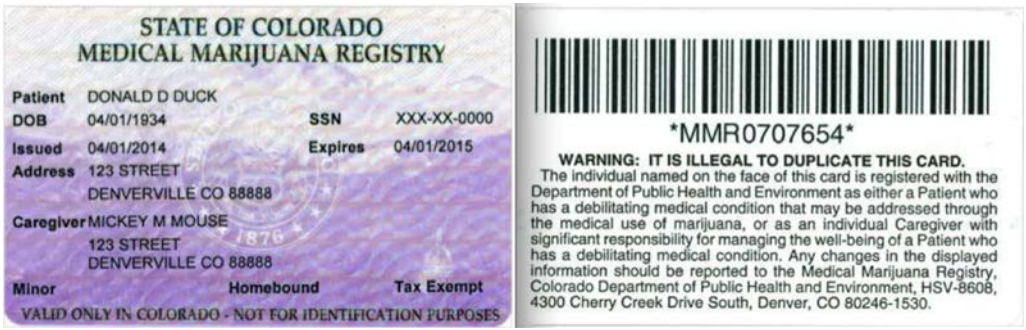
Importance of Talking about Cannabis

- Examples of questions:
  - Are you thinking about using any complimentary or alternative therapies?
  - Are you currently using any?
  - There is a lot of conversation (locally, nationally, etc) about the use of cannabis, which can be either marijuana or hemp, for patients undergoing treatment for cancer. Have you thought about that? Have any questions for our team?
  - We want to keep lines of communication open so we can all make sure that you/your child have the best outcomes and fewest side effects of therapy.

- Increased use of CBD with the Farm Bill legalizing hemp in 2018

Challenges to Treatment

- Financial
  - Clinic fee
  - Medical marijuana card
  - Product
- Social Support
  - Clinical Staff
  - Friends and Family
- Barriers
  - Travel
  - Camps
  - School Administration



Legal Questions

- Where does the patient reside?
- What age is the patient?
- Consequences for using illegally
- How to obtain a “Red Card”
- Medical Marijuana Clinics
- Dispensaries (Recreational vs. Medical)

Teach Families About Cannabis

- Every product can vary each time it is produced so encourage families to ask the dispensary the following:
  - How is it manufactured? Each method can hold traces of what is used to extract the THC and CBD. Some common ones are butane, CO2, and ethanol.
  - Ask the person (budtender, ha!) at the medical dispensary to see the testing information for a product. In Colorado they are required to send a sample of their products periodically to a lab to test for what is in it, including the concentration of THC and CBD.
  - Once you find a distributer and product you like and trust, then stick with that company/product for the best attempt at consistency in dosing.

More Teaching

- Keep a journal of dosing, reason for dosing, therapeutic effects (if desired, like for nausea), and side effects
- Include when to stop and restart cannabis that interacts with chemotherapy on a patient calendar
- Realm of Caring (https://theroc.us/)

Infection Risk

Infection risk

- Many pediatric patients with CNS tumors require chemotherapy regimens associated with immunosuppression
  - Immune cells have CB2 receptors and concern for further impact on immune function with cannabinoid use
- Unclear how “clean” procedures to prepare products from plant source that could be contaminated with bacterial and/or fungal pathogens

What you can do?

- Learn about your state's regulations
- Department of Health Website
- Cannabis Education
  - Web-based seminars
  - University offered
- Visit a clinic and dispensary
- Learn the lingo

Chemo and Cannabis Interactions

- CBD can change the metabolism of SO MANY drugs, including cytotoxic chemotherapy and targeted agents
- CBD is metabolized by cytochrome P450
- It is a strong cytochrome P450 inhibitor
- Significant risk for increasing toxicity of chemo that is also processed through this system

- THC has significantly fewer interactions than CBD (makes sense why patients can take Marinol for nausea/appetite stimulation during chemotherapy)

Chemotherapy Interactions with CBD/THC

This is not an all-inclusive list, but some of the chemotherapy agents impacted by interactions with CBD/THC include the following:

- Vincristine
- Vinblastine
- Cyclophosphamide
- Etoposide
- Irinotecan
- Ifosfamide
- Paclitaxel
- Doxorubicin
- Lomustine

Target Agents Interactions with CBD/THC

- Everolimus
- Dabrafenib
- Crizotinib
- Dasatinib
- Imatinib
- Many, many more

Resources for Marijuana Interactions

- Natural Medicines Database (https://naturalmedicines.therapeuticresearch.com/)
- Interaction rating (e.g., moderate, be cautious with this combination)
- Severity rating
- Occurrence risk (e.g., probable)
- Level of evidence
- Also contains some information on other cannabinoids like CBN

More Resources

- Régis Bouquié, Guillaume Deslandes, Hélène Mazaré, et al. Cannabis and anticancer drugs: societal usage and expected pharmacological interactions – a review. *Fundam Clin Pharmacol*. 2018;32(5): 462-484.

- Lexicomp for the metabolism/transport effects section of Lexicomp

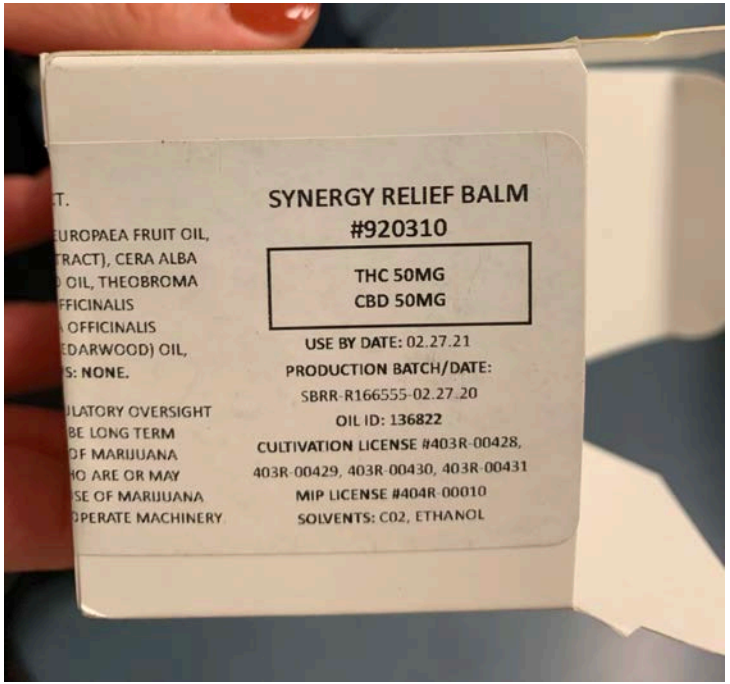
Putting it all together

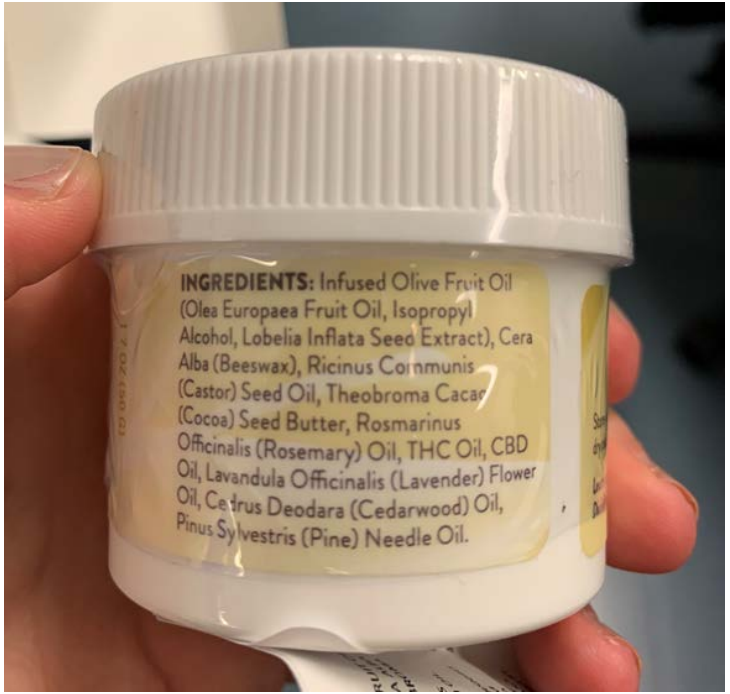
- 8 yo female, sickle cell anemia
- S/p Bone Marrow Transplant with a matched sib
- Significant mucositis pain
- Neuropathic pain in her hands
- On ketamine drip followed by fentanyl PCA, tramadol and acetaminophen
- Allergic to hydromorphone, morphine, lorazepam, oxycodone, and midazolam
- How can we help?

- Parents have used medical marijuana for her pain pre-BMT
- Concern for drug interactions with all of her BMT medications
- Goal is to wean off Fentanyl
- Discussed with BMT providers, parents, and pharmacist
- Biggest concern is keeping cyclosporin levels stable

- For mucositis, will try THC only ingested marijuana to decrease drug interactions with cyclosporin (CBD has more interactions)
- Once THC dosing to cover pain in met, let BMT team know so they can adjust cyclosporin as needed

- For neuropathic pain in her hands, will try a topical CBD salve to provide topical relief with minimal absorption to impact cyclosporin





Questions?

References

- https://www.pbs.org/newshour/science/is-cbd-legal-heres-what-you-need-to-know-according-to-science