Medical Marijuana and Stem Cell Transplant: What Do We Know?

Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023

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Learning Objectives

- Discuss marijuana legalization status in the United States
- Describe available marijuana products and the significance of route of administration
- Define marijuana's place in therapy and use in symptom management
- Review relevant and long term side effects of marijuana use in the transplant population
- Recognize pertinent drug interactions between marijuana and commonly used post-transplant medications

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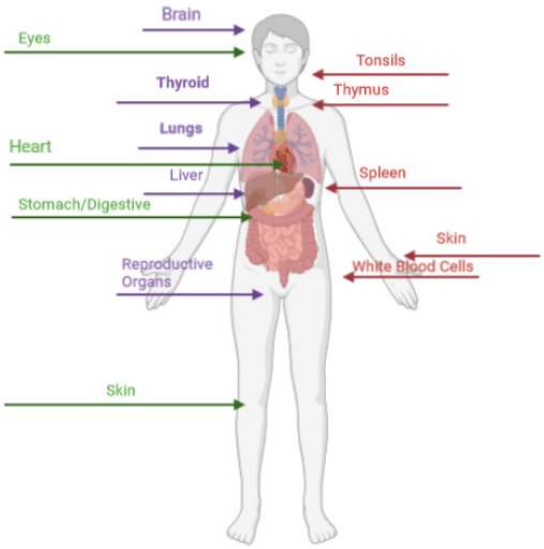
Medical Marijuana

- Extract of *Cannabis sativa*
  - Contains over 400 components
  - Over 60 are cannabinoids
- Endocannabinoids: Produced by our own body
- Phytocannabinoids: Produced by plants
  - Delta-9-tetrahydrocannabinol (THC): Psychoactive component
  - Cannabidiol (CBD)

Cannabinoid Receptors (CB_1 and CB_2)



CB_1: Purple
CB_2: Red
Both: Green

History of Marijuana

- Originated in northeastern Tibetan plateau
- Earliest use discovered in 10,000 B.C. in modern-day Taiwan
- Extensive reports of use in ancient China, India, Egypt, Africa, Greece…almost everywhere!
- Indications varied between regions

Charitos I, Gagliano-Candela R, Santacroce L, et al. Endocrine, Metabolic and Immune Disorders – Drug Targets. 2021;21:407-417

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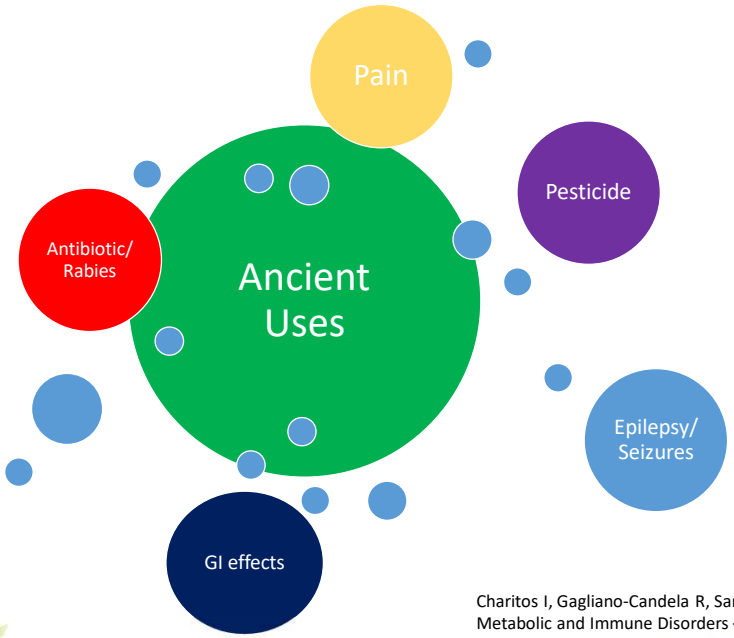

Charitos I, Gagliano-Candela R, Santacroce L, et al. Endocrine, Metabolic and Immune Disorders – Drug Targets. 2021;21:407-417

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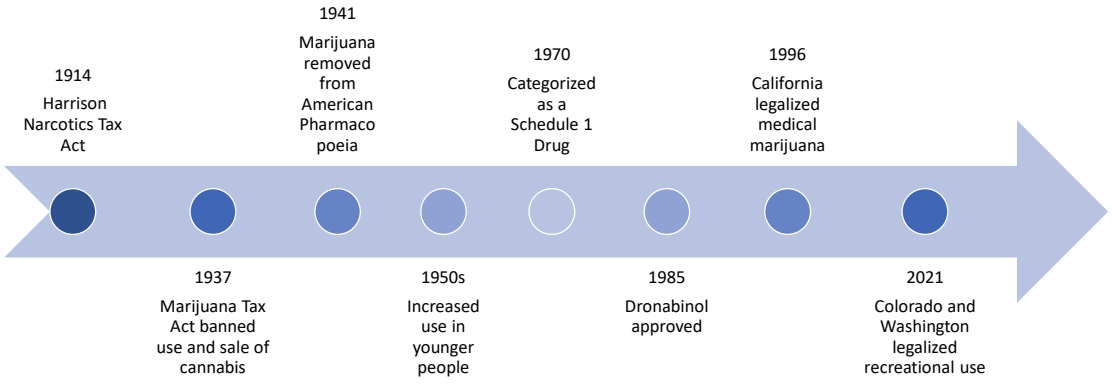
Legalization Status



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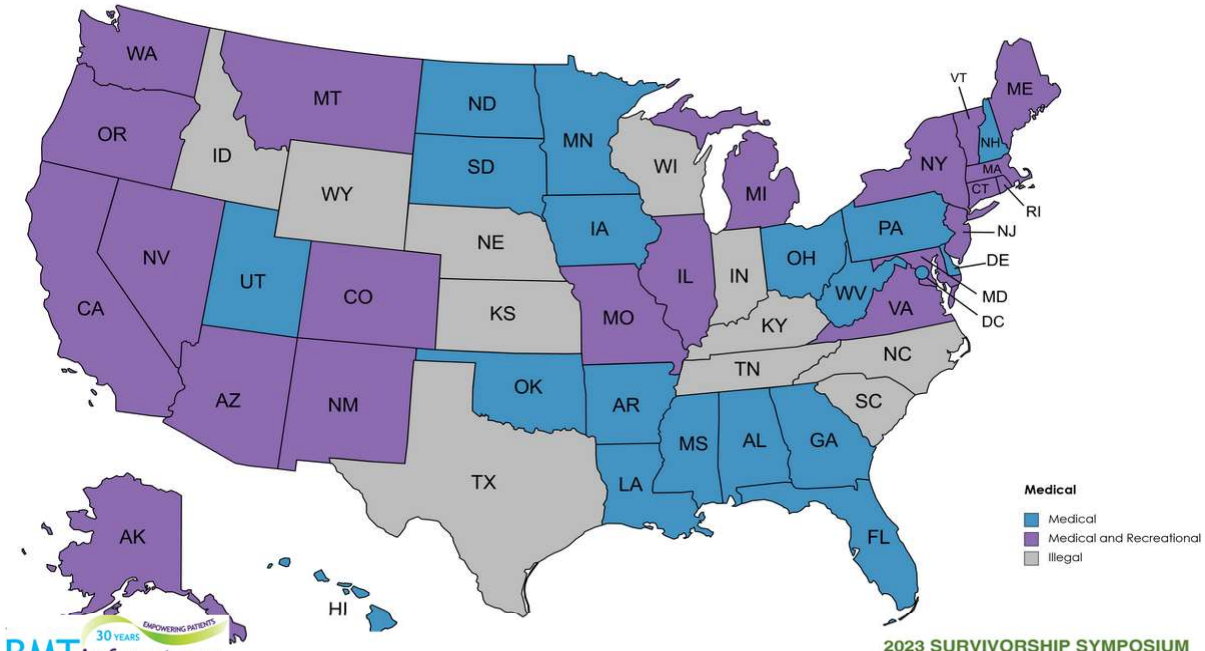

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Legalization Status

- Legal for medical use in 37 states
- Illegal under federal law
  - Schedule 1 drug
  - Cannot be prescribed, only “recommended”
- Federal restrictions make large, robust clinical studies difficult
- “Prescription” doesn’t contain doses, content, type, etc
- Not all physicians certified to prescribe

Ronne S, Rosenbaek F, Pedersen L, et al. BMC Fam Pract. 2021;22:212
Evanoff A, Quan T, Dufault C, et al. Drug and Alcohol Dependence. 2017;180:151-155

Prescribing

- Potency
  - Variable THC and CBD content
  - 50% of products don’t list CBD content
- Purity
- Dosing is unknown for most conditions
  - Start low and go slow

Mahmoudinoodezh H, Telukutla S, Bhangu S, et al. Pharmaceutics. 2022;14:438
Pennypacker S, Cunnane K, Cash M, et al. Front. Pharmacol. 2022;13:921496

Physician Comfort

- **Answering questions:**
  - Not at all: 35.5%
  - Slightly: 41.5%
  - Moderately: 15.9%
  - Very/extremely: 7.4%
- **Prescribing medical marijuana:**
  - Not at all: 89.5%
  - Slightly: 4.7%
  - Moderately: 4.7%
  - Very/extremely: 1.2%
- **Received education about medical marijuana:**
  - Not at all: 85%
  - Medical school: 8.5%
  - Residency/fellowship: 4.7%

- 50-80% of surveyed physicians believe medical marijuana should be legalized
- 70% of palliative and hospice care providers believe effective
- 67% of medical oncologists recommended as an adjunct for pain
- 50% of oncologists felt they had sufficient knowledge to recommend

Ronne S, Rosenbaek F, Pedersen L, et al. BMC Fam Pract. 2021;22:212
Evanoff A, Quan T, Dufault C, et al. Drug and Alcohol Dependence. 2017;180:151-155

Approved Products

Name	Route	Indication
Dronabinol	Oral	Anorexia (AIDS), chemotherapy induced nausea/ vomiting
Nabilone	Oral	Chemotherapy induced nausea/vomiting
Epidiolex	Solution	Seizures (Lennox-Gastaut syndrome or Dravet syndrome)
Sativex/Nabiximols Not FDA approved	Oral spray	Multiple sclerosis related spasticity

Route of Administration

Type	Route	Onset	Duration	Pearl
Flower	Smoking	Minutes	24 hours	Not recommended due risk of infection
Vaporizer/inhalers	Inhalation	1 to 10 minutes	2 to 6 hours	
Edibles/oral	Oral	30 minutes to 2 hours	4 to 24 hours	Delayed onset, hard to titrate
Creams/lotions/ tinctures	Topical	30 to 60 minutes	4 to 6 hours	(?) systemic absorption, better for local symptoms
Transdermal	Topical	1 to 20 minutes	48 hours	Variable absorption
Suppository	Rectal	15 to 30 minutes	2 to 8 hours	Not recommended if low WBCs or platelet count

WBC = White Blood Cells

CBD:THC ratio in each product varies

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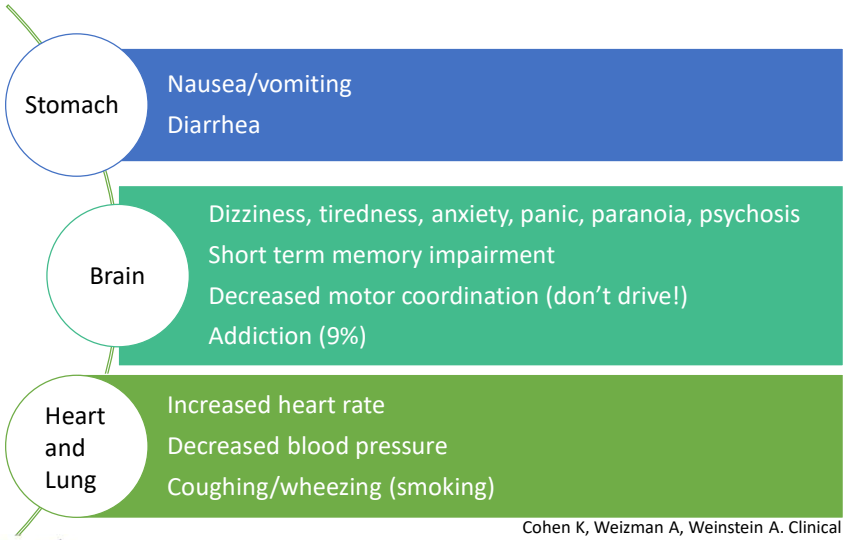
Smoking/Vaping

- Inhalation of bacteria and fungus
  - Increased risk of pulmonary infections (bacterial and fungal)
  - Aspergillus
- Deposits spores in 50% of individuals
- 3.5x more likely to develop fungal infections
- Concern most for immunocompromised patients (AKA, transplant survivors!)
  - Multiple case reports

Gargain Y, Bishop P, Denning D, et al. Mediterr J Hematol Infect Dis. 2011;3(1)e2011005
Benedict K, Thompson G, Jackson B. Emerging Infectious Diseases. 2020;26(6):1308-1310.

Side Effects



Cohen K, Weizman A, Weinstein A. Clinical Pharmacology & Therapeutics. 2019;105(5)1139-1147.

Drug Interactions

- Limited data available
- Medical marijuana is metabolized by the liver
  - THC: Inhibits CYP1A2, CYP2B6, CYP2C9, CYP2D6
  - CBD: Inhibits activity P-glycoprotein, CYP3A4 and CYP3A5, CYP2B6, CYP2D6, CYP2E1, CYP2C19, CYP2C9
  - CYP3A4 alone is involved in the metabolism of 50% of medications!

Lopera V. Rodriguez A, Amariles P. J Clin Med. 2022;11(1154).

Drug Interactions – Major Concerns

- ↑ levels of a transplant medication = ↑ toxicity/side effects
- ↓ levels of a transplant medication = ↑ risk of medication not working
- ↑ levels of medical marijuana = ↑ toxicity/side effects

GVHD Medications

Medication	Marijuana's Effect	Effect on GVHD Medication
Tacrolimus	Prevents metabolism (↑ levels)	↑ side effects
Cyclosporine	Prevents metabolism (↑ levels)	↑ side effects
Sirolimus	Prevents metabolism (↑ levels)	↑ side effects
Mycophenolate Mofetil (Cellcept®)	None	None
Prednisone	Prevents metabolism (↑ levels)	↑ side effects
Ruxolitinib (Jakafi®)	Prevents metabolism (↑ levels)	↑ side effects
Belumosudil (Rezurock®)	Prevents metabolism (↑ levels)	↑ side effects
Ibrutinib (Imbruvica®)	Prevents metabolism (↑ levels)	↑ side effects

Clinical significance unknown, consult with your doctor before starting

Anti-Infectives

Medication	Interaction Effect	Effect
Posaconazole	↓ marijuana metabolism	↑ marijuana side effects
Voriconazole	↓ marijuana metabolism	↑ marijuana side effects
Acyclovir	None	None
Valacyclovir	None	None

Clinical significance unknown, consult with your doctor before starting

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Maintenance Medications (ALL/CML)

Medication	Marijuana's Effect	Effect on Maintenance Medication
Imatinib (Gleevec®)	Prevents metabolism (↑ levels)	↑ side effects
Dasatinib (Sprycel®)	Prevents metabolism (↑ levels)	↑ side effects
Nilotinib (Tasigna®)	Prevents metabolism (↑ levels)	↑ side effects
Bosutinib (Bosulif®)	Prevents metabolism (↑ levels)	↑ side effects
Ponatinib (Iclusig®)	Prevents metabolism (↑ levels)	↑ side effects
Asciminib (Scemblix)	Prevents metabolism (↑ levels)	↑ side effects

Clinical significance unknown, consult with your doctor before starting

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Maintenance Medications (AML)

Medication	Marijuana's Effect	Effect on Maintenance Medication
Venetoclax (Venclexta®)	Prevents metabolism (↑ levels)	↑ side effects
Gilteritinib (Xospata®)	Prevents metabolism (↑ levels)	↑ side effects
Sorafenib (Nexavar®)	Prevents metabolism (↑ levels)	↑ side effects
Azacitidine (Onureg®)	None	None
Enasidenib (Idhifa®)	Prevents metabolism (↑ levels)	↑ side effects
Ivosidenib (Tibsovo®)	Prevents metabolism (↑ levels)	↑ side effects

Clinical significance unknown, consult with your doctor before starting

Lopera V. Rodriguez A, Amariles P. J Clin Med. 2022;11(1154).

Place in Therapy

Place in Therapy

- Not recommended first line
- Consider as an add on in the third line setting
- Not enough data, limited trials of good quality
  - Small trials, increased risk of false positives
  - Not blinded, increased risk of placebo effect
  - Follow up time not long enough
- Variable doses/preparations
- Most studies use FDA approved products

Whiting P, Wollf R, Deshpande S, et al. JAMA. 2015;313(24):2456-2473.
Allan M, Ramji J, Perry D, et al. Canadian Family Physician. 2018;64:111-120.

Nausea/Vomiting

- Not recommended as first or second line therapy
- Consider as an "add on agent" third line
- Recommend nabilone or dronabinol
- Multiple studies (mostly dronabinol/ nabilone)
- No data to suggest its more effective than initial therapy
- Benefit compared to placebo or other anti-nausea medications (prochlorperazine, chlorpromazine, etc) in refractory nausea/vomiting

Whiting P, Wollf R, Deshpande S, et al. JAMA. 2015;313(24):2456-2473.
Allan M, Ramji J, Perry D, et al. Canadian Family Physician. 2018;64:111-120.

Cancer Pain

- Not recommended as first or second line therapy
- Consider as an "add on agent" third line
- Recommend nabilone or nabiximol (not FDA approved) over medical marijuana
- Multiple trials evaluating various products against placebo or opioids
  - Reduction in pain scales when compared to placebo
  - Less clear benefit when compared to opioids
    - Similar reduction in pain scores to opioids or opioids had higher reduction in pain scales
- Varying products/doses studied, not clear which is best

Allan M, Ramji J, Perry D, et al. Canadian Family Physician. 2018;64:111-120.
Aviram J, Samuelly-Leichtag G. Pain Physician. 2017;20:E755-E796.
Johnson J, Lossignol D, Burnell-Nugent M, et al. J Pain Symptom Management. 2013;26(2):207-218.
Portenoy R, Ganae-Motan E, Allende S, et al. Journal of Pain.2012;13(5):438-449.

Peripheral Neuropathy (Pain)

- Several larger studies looking at cannabis cigarettes/vaping found lower pain scores when compared to placebo
  - Strongest studies in HIV
  - Studies were all short duration
  - Most were THC dominant strains
- Mixed results in trials with nabiximol and cannabis extracts
- Not recommended. Can consider as an "add on agent" third line

Whiting P, Wollf R, Deshpande S, et al. JAMA. 2015;313(24):2456-2473.
Mucke M, Weier M, Carter C, et al. Journal of Cachexia, Sarcopenia and Muscle. 2018;9:220-234.
Allan M, Ramji J, Perry D, et al. Canadian Family Physician. 2018;64:111-120.

Anorexia/Cachexia

- Most data is in AIDS-related anorexia
  - Trend towards increase in weight, increased appetite but most were not considered statistically significant
- Cannabis extract + THC compared to placebo in cancer-related anorexia/cachexia showed no benefit
- Dronabinol compared to megestrol: Megestrol was superior to dronabinol promoted weight gain and appetite
  - Patients on the dronabinol arm did gain weight/increase appetite
- May be beneficial in some patients as a third line agent

Strasser F, Luftner D, Possinger K, et al. JCO. 2006;24:3394-3400.
Jatoi A, Windschitl HE, Loprinzi CL, et al. JCO. 2002;20:567-573.

Depression/Anxiety

- No robust trials in depression
  - Four trials evaluated depression in chronic pain study
    - Used nabiximol or nabilone
  - No difference compared to placebo
    - One trial favored placebo with higher doses of nabiximol
- Anxiety
  - Trial of 24 patients with generalized social anxiety disorder reported improvement in anxiety based on scale
  - Chronic pain studies report improvement in anxiety compared with placebo
- Not recommended for treatment of anxiety or depression

Whiting P, Wollf R, Deshpande S, et al. JAMA. 2015;313(24):2456-2473.
Allan M, Ramji J, Perry D, et al. Canadian Family Physician. 2018;64:111-120.

GVHD Prophylaxis

- Trial adding cannabidiol 300 mg orally for 48 patients who got a matched donor (sibling) transplant to prevent GVHD
- Cannabidiol 300 mg orally day -7 to day +30
  - Also got methotrexate and cyclosporine (standard for transplant)
- No severe side effects with cannabidiol
- Acute GVHD rates were lower than historical patients
  - Overall: 12%
  - Severe acute GVHD: 5%

Yeshurun M, Shpilberg O, Herscovici C, et al. BBMT. 2015;21:1770-1775.

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BUT…

- THC, CBD and cannabis extracts prevented certain white blood cells (lymphocytes) reconstitution in animal models
- Increased risk of infections, graft issues, etc
- No human studies available

Almogi-Haza O, Khuja I, Ritter S, et al. Rambam Maimonides M J. 2020;11(1):e0009.

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So can I use it?

- Recommend avoiding for the first months after transplant to allow white blood cell recovery
- Talk with your doctor about adding for symptom management
- Use as an add on medicine if front line agents don't work
- Start low and go slow
- Don't smoke it!

Future Directions

- Over 200 ongoing trials
- FDA reviewing scheduling of cannabis

QUESTIONS?

Alison Carulli, PharmD, BCOP
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LET US KNOW HOW WE CAN HELP YOU

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Email us: help@bmtinfonet.org

Give us call: 888-597-7674 or

847-433-3313