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

Celebrating a Second Chance at Life
Survivorship Symposium

April 17- 23, 2021
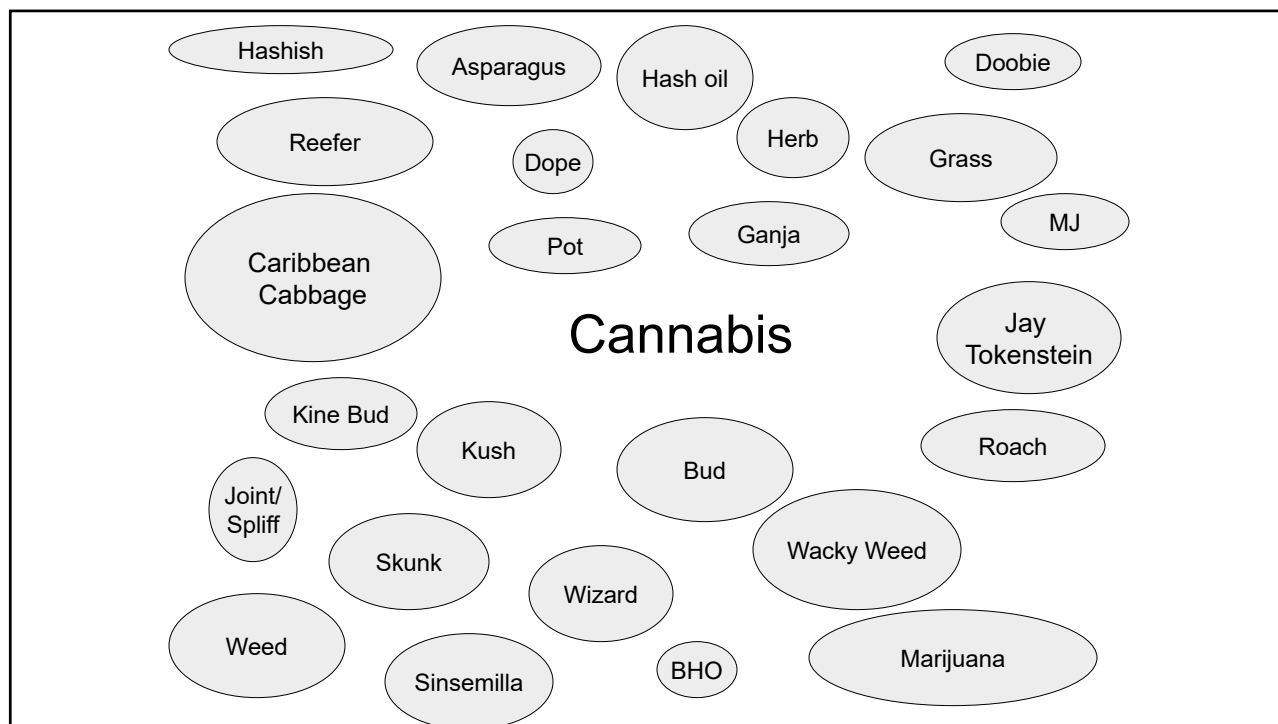
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# Medical Marijuana and Stem Cell Transplant…. What Do We Know?

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Hashish

Asparagus

Hash oil

Doobie

Reefer

Dope

Herb

Grass

Caribbean
Cabbage

Pot

Ganja

MJ

Cannabis

Jay
Tokenstein

Kine Bud

Kush

Bud

Roach

Joint/
Spliff

Skunk

Wizard

Wacky Weed

Weed

Sinsemilla

BHO

Marijuana

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# At the conclusion of this workshop attendees should have a clear understanding of the following:

- The probable mechanism by which cannabis products affect mood and physical discomfort

- How quality and potency of cannabis varies, depending on source

- Potential benefit, if any, for HCT survivors to use medical cannabis

- Potential adverse effects and drug interactions associated with the use of medical cannabis

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# Listed in U.S Pharmacopeia 1850-1941

- Marijuana and hashish extracts were the 1st, 2nd, or 3rd most prescribed meds in the US from 1842-1890s

- Labor pain, nausea, rheumatism

- Criminalized in 1914, 1937, 1951, schedule I in 1970

- 2018 first non-synthetic cannabis product approved

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# Marijuana

Cannabis sativa – flowering herbal plant

- Also refers to indica and ruderalis species

- Originated in Asia, now grown nearly worldwide

- Currently >30 states + D.C. have programs authorizing cannabis use for specific medical conditions

- Additional 14 states allow Low delta 9 tetrahydrocannabinol (THC), High cannabidiol (CBD) products for qualifying medical reasons

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# Cannabis Compounds

- Terpenes (Terpenoids)
  - Aromatic chemicals also found in pine trees, citrus flora, and other odoriferous plants
  - Produce the unique aroma and flavor of cannabis
- Flavonoids
  - Chemicals common to most plant life
  - Many considered to have anti-inflammatory and antioxidant properties
- (Phyto)Cannabinoids
  - Highest concentration found in female flowers
  - Bind to cannabinoid receptors and change body response

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# Common Cannabinoids in Use

- Delta-9-tetrahydrocannabinol (THC)
  - Major psychoactive component in cannabis
  - Naturally occurs in concentrations anywhere from 0.5 – 20% depending on cannabis cultivar and how processed
- Cannabidiol (CBD)
  - Lacks any noticeable psychoactive affects- may decrease anxiety
  - Does not interact with cannabinoid receptors
  - Modulates the action of/exposure to THC
- Over 140 different cannabinoids found in cannabis

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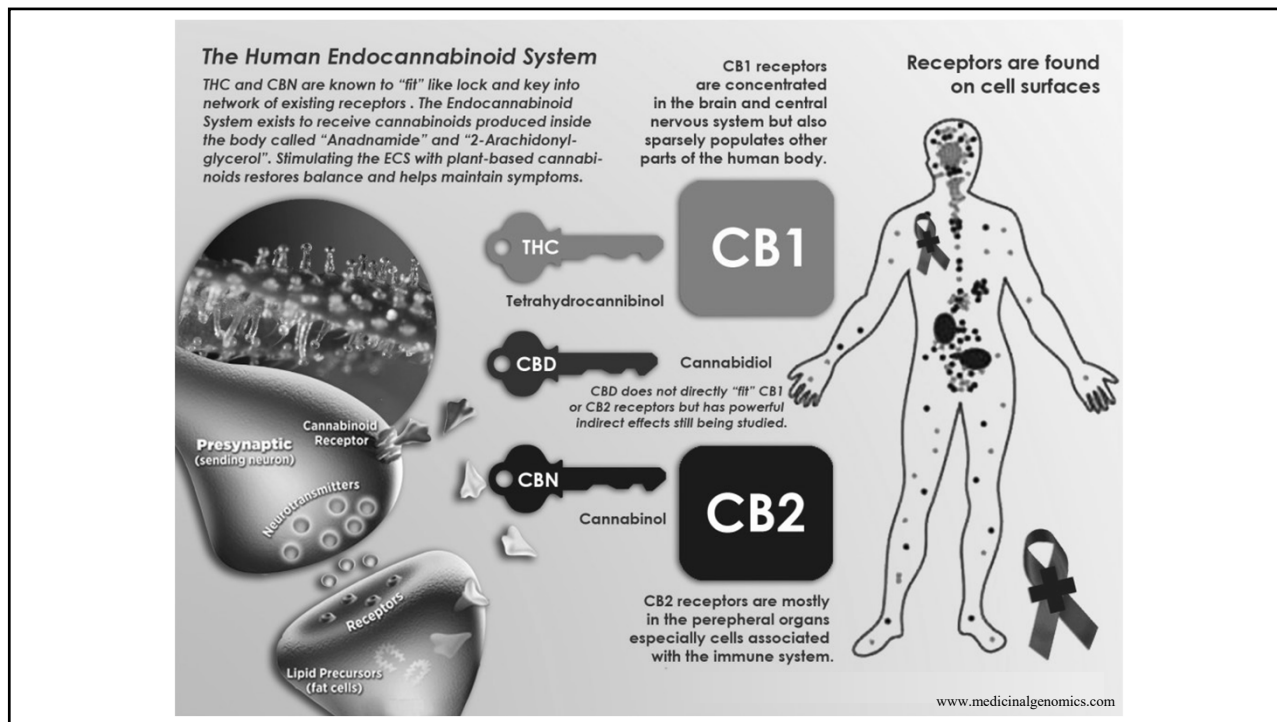
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# Dosing Notes

- Generally, 2-3 mg smoked for average "high"

- Oral dose must be 3-5 times the inhaled dose due to stomach acid effects and liver first-pass metabolism.

  – Delayed and erratic onset times

- Smoked onset occurs in minutes while oral can take an hour or longer

- Oregon has 5 mg increments in a "dose"

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# Drug Interactions

- Interactions with prescription medications common

  – Interacts with body metabolism systems

- Dynamic interactions

  – Additive effects to sedating agents

    ▪ Sleeping pills, antihistamines, antianxiety agents and others

  – Opposing effects to stimulants

  – Antidepressants and psychiatric drugs – variable

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# Cannabis Pharmaceuticals

Dronabinol (Marinol®)

- Synthetic Δ9-THC in sesame oil

- Activates cannabinoid receptors $CB_1$ and $CB_2$; has approximately equal affinity for each, but efficacy is less at $CB_2$ receptors

Nabilone (Cesamet®)

- Synthetic THC that binds both CB1 and CB2 receptors

Cannabidiol (Epidiolex®)

- Purified cannabidiol from cannabis plants as a 100 mg/mL oral solution

- Does not bind to the CB1 or CB2 receptor

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# Cannabidiol (CBD)

- Hemp-derived (maximum 0.3% THC)

- Marijuana-derived (5-30% THC common)

- Pharmaceutical-derived

  - Epidiolex: FDA Approved, plant derived, available nationally, < 0.1% THC

- All from Cannabis sativa, but cultivar predicts for content

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# Common Cannabis Preparations

- Marijuana – dried leaves, stems, flowers

- Hashish – Concentrated resin, may come as a cake

- Tincture –liquid infused with cannabinoid

- Oil – extracted from the plant with a variety of solvents (butane, $CO_2$, ethanol, propane, etc.), different names

- Infusion – cannabis plant material mixed with nonvolatile solvent (butter, cooking oil, etc.)

- Edibles – Wide variety of choices in solid and liquid form

- Hemp products – primarily provide CBD, may have variable THC.

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# Natural Product Issues

- Purity – (herbicides, pesticides)

    – Some states testing for these

- Potency (THC content, other cannabinoid content)

    – All studies thus far show >50% of products are mislabeled

- Each batch, even of the same cultivar, will have different contents

- Appropriate medical dose per condition is unknown

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# Synthetic Cannabinoids

- Emerged in the early 2000's

- Group of compounds that interact with the endocannabinoid system

- 7 major chemical/structural groups

    – Spice, K2, Fake Pot, etc.

- Now schedule I

- Multiple cases of acute kidney injury with use, ongoing contamination and mislabeling issues

- Variable and unknown toxicity profile

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# Medical Use of Cannabis

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# Cannabinoid Effects

Activation of cannabinoid system causes four groups of psychological effects

- Affective: euphoria and easy laughter

- Sensory: time and space perception altered and disorientation common

- Somatic: drowsiness, dizziness, and poor motor coordination

- Cognitive: confusion, memory lapses, and difficulty concentrating

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# Potential Uses for Medical Marijuana

- Pain
- Nausea
- Cancer
- Anorexia/cachexia
- Neuropathy
- Glaucoma
- Seizures
- Depression and anxiety

- Insomnia
- Muscle spasms
- Migraines
- Post traumatic stress disorder
- Agitation related to Alzheimer's disease
- Anti-mania/bipolar disorder

Whiting et al. *JAMA.* 2015;313(24):2456-2473.

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*JAMA.* 2015;313(24):2456-2473.

Research

Original Investigation

## Cannabinoids for Medical Use
### A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

BJCP British Journal of Clinical Pharmacology

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## Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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INVITED REVIEW

## Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch[1,3] · Mark A. Ware[2]

Published online: 22 March 2015

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## Author Conclusion

Meta-analysis including 79 randomized controlled trials of cannabis across a broad range of conditions

- Most evaluated prescription cannabinoids (dronabinol, nabilone, nabiximols)

- moderate-quality evidence to support the use of cannabinoids for the treatment chronic nerve-caused or cancer pain (smoked THC and nabiximols)

- Limitations: short study length, differing outcome measures, lack of blinding, crossover trials were not included in analysis

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# Is There Harm from Cannabis?

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# Hard Drugs vs. Soft Drugs

Soft drugs

- Less addictive

- Less dangerous - either side effects or lethality

- Overdose risk of marijuana is very small in comparison to other recreational medications

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# Cannabis Side Effects*

| Product | Dronabinol | Nabilone | Cannabidiol | Marijuana |
|---|---|---|---|---|
| Abnormal thinking | 3-10% | 2% | NR | Common |
| Appetite Increase | FDA use | 2% | -13-28% | Common |
| Diarrhea | <1% | <1% | 19-31% | NR (constipating) |
| Dizziness | 3-10% | 59% | NR | Common |
| Emesis | 3-10% | <1% | 10-15% | NR |
| Euphoria | 8-24% | 11-38% | NR | Common |
| Fatigue | <1% | <1% | 20% | NR |
| Hypotension | <1% | 8% | NR | Common inc. orthostatic |
| Infection | NR | <1% | 11% (URI) | Reported |
| Nausea | 3-10% | 4% | NR | NR |
| Somnolence | 3-10% | 3-66% | 15-36% | Drowsiness |
| Visual changes | <1% | 13% | NR | Common |

* Side effects dose related, NR=not

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# Smoke or Vape?

- Cannabis is usually smoked without a filter, and smoking dynamics studies among habitual marijuana users show that the overall burden of particulates delivered to the respiratory tract is about 4 times greater when smoking marijuana than when smoking the same amount of tobacco

- Smoked: Combustion at 600-900°C produces toxic biproducts:

  – tar, hydrocarbons, carbon monoxide and ammonia

- Vaporized: Combustion at 160-230 °C reduces carbon monoxide but some hydrocarbons remain

- Vaping is theoretically superior to smoking regarding less harmful byproducts and decreased pulmonary symptoms

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# Non-Cancer Respiratory Effects

- Wheezing, sputum production and chronic cough but not COPD

- Inhalation of smoke or vaporized cannabis increases risk of pulmonary infections

  – Most common bacteria = Enterobacteriaceae

  – Most common mold = Aspergillus

- Danger is primarily to the immunocompromised host

  – Dry buds more dangerous than oil

- Many medical case reports; a fatal outcome in some

- Sterilization techniques exist, but are not routine in the USA

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# Dose Dependent Relationship Between Cannabis Smoking and Lung Cancer

- Retrospective case-control study in New Zealand assessed the risk of lung cancer as it relates to joint-years and other variables

- Risk of lung cancer increased 8% for each joint-year of cannabis smoking and 7% for each pack-year of cigarette smoking

- Joint year = 1 joint/day/year

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# Cardiac and Cerebrovascular Effects

- Many medical reports of different kinds

- Acute dosing associated with

    ↑ heart rate   ↑ cardiac output   ↑ blood pressure

- Case reports of sudden cardiac death or stroke in young people (men) with no/few risk factors

- Risky in people with angina, arrhythmia or other cardiac or stroke risks, particularly risky with concentrated products to cause heart attacks or strokes

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# Cannabis in Adolescents

- Endocannabinoid system critical in brain development and maturational processes

- Adolescent exposure causes long-lasting alterations in the endocannabinoid system and other neurotransmitter systems

  - Linked to affective, behavioral, cognitive, and neurochemical consequences lasting into adulthood

- Brain development continues until age 25 years

  - Legal sales to persons aged 21 years or older

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# Potential Reproductive Harms

- Animal studies show growth retardation and fetal malformations

- Most human studies confounded by concomitant tobacco, alcohol, or other illicit drug use

  - Appears to result in lower birth weight at the very least

- Delayed visual system development, increased tremors

- Lower scores in memory and verbal outcomes seen along with increased rates of delinquency and problem behaviors at age >10

- Prenatal exposure is a risk factor for adolescent mental health issues

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# Dependence

- Public opinion considers cannabis non-addictive, especially when ingested orally rather than inhaled

  - dependence is common in some as the brain develops a tolerance to cannabinoids

- Dependence develops in 9-10% of cannabis users

- Risk lower than nicotine (32%), heroin (23%), and alcohol (15%), and equivalent to anxiolytics (sedatives) and cocaine (11%)

- Physiologic withdrawal after long-term use is common

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# Driving

- Doubles rate of auto accidents in multiple studies

- Dose related effects to coordination and judgment with more marked effects on automated functions of driving vs. those with cognitive control

  - Tendency to overestimate impairment and many appear to be able to compensate to some regard

- 12% increase in fatal car crashes on 4/20 vs 1 week before or after

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# Fungal Infections

- Multiple cases of pulmonary aspergillus infections in oncology patients

  – Solid tumor, hematologic malignancy, and BMT

- Case reports in non-oncology patients

  – Tends to be associated with longer use and only with smoking marijuana thus far

- Smoking marijuana deposits spores in about 50% of individuals

- Medical sterilization processes successful but no commercial delivery device sterilizes cannabis

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# Cannabis and the Immune Compromised

- Inhalation of smoke or vaporized product result in direct inhalation of bacteria and molds from plant surfaces.

- Cannabis and tobacco commonly contaminated

  – Aspergillus most concerning

- Cannabis products can be sterilized via autoclave, plasma $H_2O_2$, and ethylene oxide with some loss of THC.

- Home baking 300 degrees F x 50 minutes generally effective with unclear amount of THC loss

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# Cannabis is currently framed as
# 3rd line for medical use or later, not 1st line

An appropriate candidate should have:

- A debilitating medical condition that data from trials suggest would respond to medical marijuana (e.g., N/V associated with cancer chemotherapy, anorexia from  wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis)

- Multiple failed trials of first- and second-line therapies for these conditions

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# Cannabis is currently framed as
# 3rd line for medical use or later cont'd

- A failed trial of a US FDA approved cannabinoid (dronabinol or nabilone) if clinically appropriate

- No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder. Warn about anxiety.

- Residence in a state with medical nurse practice act  and medical marijuana laws and meets requirement of these laws

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# Take Home Points - Risk

- Unclear risk for lung cancer

  – vaping **may** confer lower risks than smoking

- Multiple published case studies regarding CVD/CAD risk, but no serious AEs in controlled trials

- Use in psychiatric disorders concerning

  – No clear benefit in any psychiatric disorder, harm likely in schizophrenia and bipolar

  – Dose dependent relationship between cannabis and psychosis and schizophrenia, particularly with adolescent/young adult exposure

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# Take Home Points – Risk cont'd

- Less habit forming than nicotine and 'hard drugs' but dependence risk is real (~9%), particularly in adolescents

- Prenatal exposure is problematic

- Need studies in higher risk subgroups (older adults with chronic illnesses)

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# Take Home Points – Benefits?

- True medical benefits unclear

- Areas of Promise

  – Pain relief, especially neuropathic pain

  – Muscle disorders

  – Seizure disorders

  – Appetite and nausea

  – "Mood"

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Questions?

Spell Caster, Kimbo Kush, Dream Dog, Cornbread, Power Nap, Snow Leopard, Koala, Real McCoy, Silver Tip, Wedding Cake Bud, POG, OG Kush, Maui Waui, Critical Mass, Star Killer, Nuken, Moon Puppy, Strawberry Satori, Sunset Sherbert, Life Me Up, Extreme Cream, Triangle Dragon, Zam Skunkband, Lime Squeeze, Corazon, Buzzed Aldrin

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# Therapeutic Cannabis Dosing

- Start low and go slow
- "U" shaped effect curve
- Oral dosing
  - Initial dose 2.5 mg (THC content)
  - 5 mg moderate
  - 10 mg strong
  - 15 mg increased risk of adverse effects
  - Questionable benefits for doses > 25 mg depending on use
- No current guidance for CBD- "threshold dose"

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# Edibles (medibles)

75 products analyzed for labeling accuracy with respect to THC and CBD content

- 17% were accurately labeled
- 23% were underlabeled
- 60% were overlabeled

| Type of Cannabinoid | Cannabinoid Content, mg | |
|---|---|---|
| | Median (IQR)[a] | Range |
| Tetrahydrocannabinol | 54 (99) | <1-1236 |
| Tetrahydrocannabinolic acid | 2 (15) | <1-173 |
| Cannabidiol | 2 (3) | <1-51 |
| Cannabidiolic acid | 1 (5) | <1-20 |
| Cannabigerol | 3 (3) | <1-43 |
| Cannabinol | 2 (2) | <1-20 |

  - Median THC:CBD ratio of products with detectable CBD was 36:1
    - 7 had ratios of <10:1
    - 1 had a 1:1 ratio
  - Need for child resistant packaging

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# Cannabidiol Extract Labeling Accuracy

| Product | Oil (n=40) | Tincture (n=20) | Vaporization Liquid (n=24) | Total |
|---|---|---|---|---|
| Accurate | 45% (18) | 25%(5) | 12.5%(3) | 31%(26) |
| Under | 25%(10) | 40%(8) | 75%(18) | 42.9%(36) |
| Over | 30%(12) | 35%(7) | 12.5(3) | 26.2%(22) |

Accurate = within 10% of stated amount

- Products purchased from online retailers 9/16-10/16, blinded and sent to an independent lab
- THC up to 6.43 mg/mL found in 18 samples (21.43%)

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# Product Issues: In the News

- Idaho – Synthetic cannabinoid labeled as CBD[1]

- Illinois – synthetic cannabis (plant matter sprayed with K2) contaminated with rat poison – 3 deaths, 116 severe bleeding

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## Oral Cannabis Notables

- Not all cooking temperatures sterilize cannabis and the heat stability of the different compounds is unclear.

- All cannabinoids are degraded by heat labile with differing levels of loss during heating

- Lower risk for pathogen contamination overall depending on adherence to food handling rules

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## Sterilizing Cannabis

- Initial cultures yielded enterobacteriaceae and a mixture of molds, primarily aspergillus.
- Cookies, dried buds, and SubLingual oil were compared pre and post sterilization
  - Cookies – limited contamination risk
- All 3 methods were able to sterilize the product with associated THC loss
  - Plasma 12.6%
  - Ethylene oxide 26.6%
  - Autoclave 22.6%
- Irradiation doesn't appear to diminish cannabinoids
- Oregon tests for water content as opposed to molds

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# Questions?

Celebrating a Second Chance at Life Survivorship Symposium 2021

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