What Providers Should Know About Patients Using Cannabis

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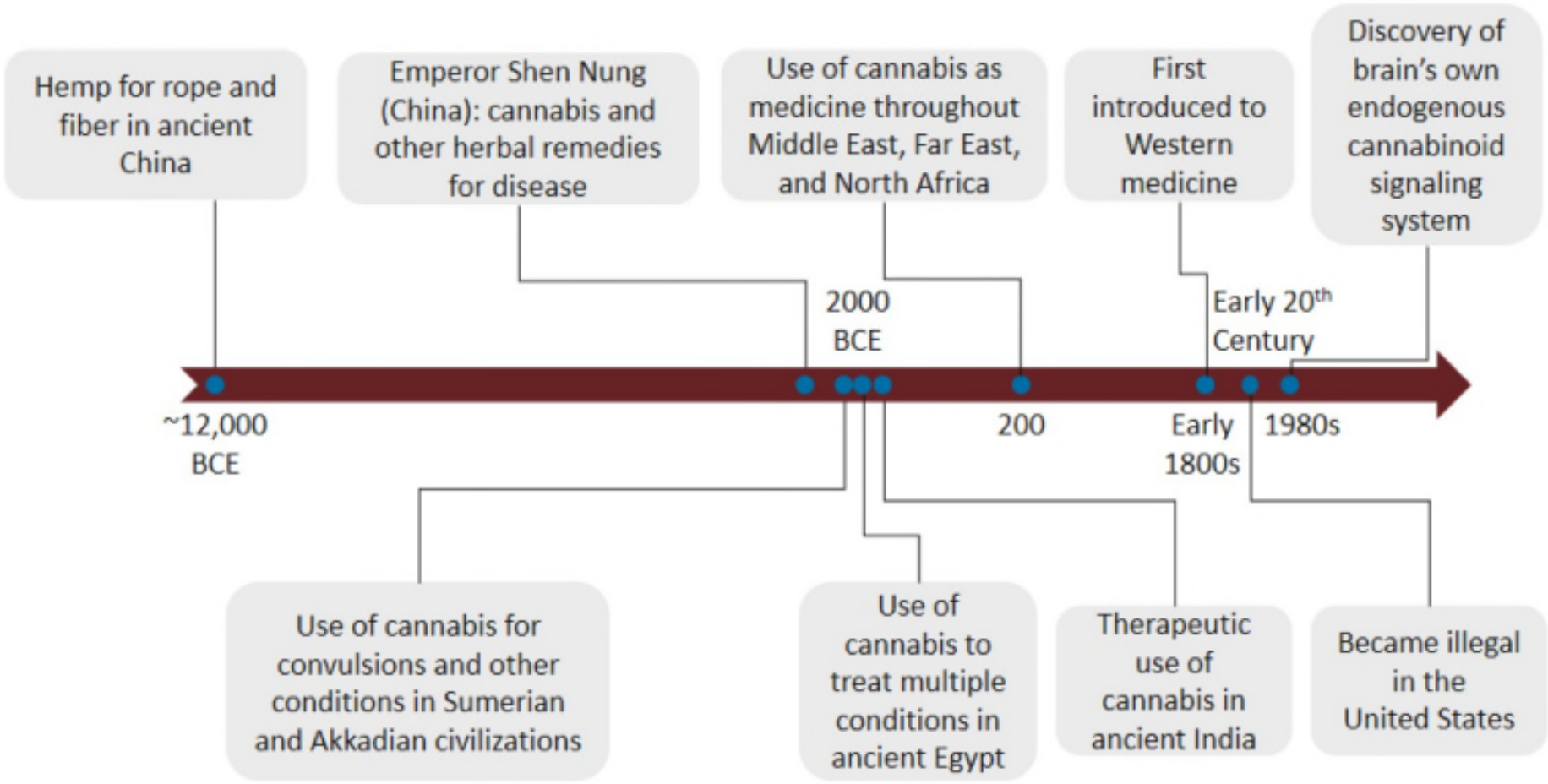
Objectives

1. Overview & understanding of cannabis products; availability and access
2. Awareness of potential drug interactions with cannabis
3. Evidence of Efficacy / Inefficacy
4. Discussion of “complementary alternative medicines” (CAM); cannabis use; documentation in medical chart
5. Talking points for patients using cannabis

History of Cannabinoid Use in Medicine



Pharmaceutical- vs Dispensary-Sourced Cannabinoids: What's the Difference?
Authors: Daniel Friedman, MD, MSc; Anup D. Patel, MD

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Cannabis Background

Cannabis = synonym for marijuana

FDA Approved, Recreational (Adult-Use) &

Medical Marijuana (MMJ)

Federal:

- Schedule I in the US
- US federal law prohibits all possession, sale, and use of marijuana
- Most parts of the cannabis plant and its derivatives *(exception: Hemp derived CBD is legal < 0.3% THC)*

Massachusetts:

- *Cannabis Control and Advisory Board* - ensures safe access to marijuana; may possess 1 oz./10 oz. at home

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Cannabis Plant Family

3 major species :

- *cannabis sativa* (most common, highest level of THC)
- *cannabis indica* (typically more CBD than THC)
- *cannabis ruderalis* (few psychogenic properties)

3 major types of cannabinoinds; > 100 chemical entities:

Plant (phytonacannabinoids) Synthetic Endogenous

Phytonacannabinoids - therapeutic activity

- **THC (delta-9-tetrahydrocannabinol)** psychotropic activity
- **CBD (cannabidiol)** non-psychotropic activity
- Terpenes – responsible for smell and taste of cannabis

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How Cannabis Works

Endocannabinoid System (ECS) – Internal Homeostatic System

- plays a critical role in the nervous system
- regulates multiple physiological processes including:
  - modulation of pain, appetite, digestion, mood & seizure threshold
  - influences immunomodulation, cardiovascular functions, sensory integration, fertility, bone physiology, the hypothalamic-pituitary-adrenal axis, neural development & intraocular pressure

Cannabinoids block/stimulate receptors in ECS

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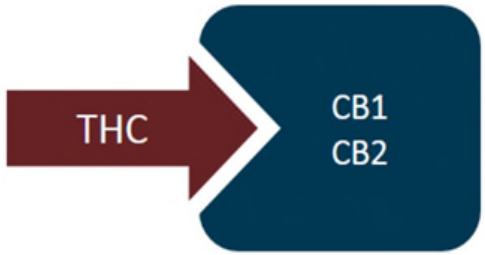
THC (delta-9-tetrahydrocannabinol) Pharmacology

THC binds to exogenous CB1 and CB2 receptors:

- CB1 receptors in CNS (brain, spinal cord, hippocampus, cerebellum, peripheral nerves)
- CB2 receptors outside the brain, immune system and peripheral cells



Activation of these receptors cause:

- euphoria
- impaired memory/cognition
- reduced locomotor function
- analgesic
- sleep-promoting effects
- psychosis
- antiemetic
- increased appetite
- ant spasticity

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CBD (cannabidiol) Pharmacology

CBD - low affinity for CB1 receptors (non-psychogenic)

Activation of these receptors:

analgesia	anti-inflammatory (decrease pain)
anxiolytic	antiepileptic
antipsychotic	

Pharmaceutical vs Dispensary Sourced Cannabinoids ; What's the Difference Medscape Education CME Released March 21, 2018

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FDA Approved Products

Synthetic (THC based)

Dronabinol (III)

- *Marinol* synthetic version of THC (2.5 mg, 5 mg, 10 mg capsules) ~$800 #60
- *Syndros* 5mg/ml 30ml ~ $1400
- Tx of refractory CINV ; anorexia associated weight loss in patients with AIDS
- Off label: Sleep apnea

Nabilone (*Cesamet*) (II)

- Chemically similar to THC (1 mg capsule) $2000 #60
- Tx of refractory CINV

Plant (CBD based)

Cannabidiol (*Epidiolex* - anticonvulsant)(V); purified CBD 100mg/ml -

- Tx certain types of refractory childhood-onset seizures due to Dravet & Lennox-Gastaut syndromes

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Other Synthetic Products

Combination products: CBD and THC

Nabiximols (currently Canada only) (*Sativex*)

- Standardized extract of *Cannabis sativa* (Oromucosal/buccal spray for SL use) (Each 100 mcg spray delivers 2.7 mg THC and 2.5 mg CBD)
- Only agent indicated for adjunctive tx of neuropathic pain from MS or cancer pain
- Not yet approved in the US

CBD and THC (*Tilray* 2:100 [Canada only])

- used to treat certain types of refractory childhood-onset seizures due to Dravet and Lennox-Gastaut syndromes

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Recreational (Adult-Use) Cannabis

Unregulated ratios of THC to CBD

THC concentration in plants varies based on cultivation and manipulation of plants

1980s – THC 3%

2009 – averaged 13%

Now – ranges from 15% to 20%; up to 37%

Massachusetts:

- Taxed; > 21 years can purchase (State Sales 6.25%, State Excise Tax 10.75% and cities /towns up to 3%)
- Some regulation for safety and efficacy
- Possession: 1 oz. on person / up to 10 oz. in home grow up to 6 plants home

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Medical Cannabis /Marijuana (MMJ)

Higher ratio of CBD to THC; fewer psychoactive effects

Plant species (sativa, indica or hybrid) - cultivated under quality controlled / reproducible THC & CBD levels

Strictly regulated for product safety /efficacy

Assayed for: cannabidilols; heavy metals; pesticides etc.

Massachusetts:

- Not taxed
- MA resident; ≥ 18 years old
- < 18 years requires 2 MA licensed certifying MDs
- Cannabis card; physician certification not Rx

https://www.mass.gov/lists/medical-use-of-marijuana-laws-regulations-and-guidance#guidance-for-health-care-providers-

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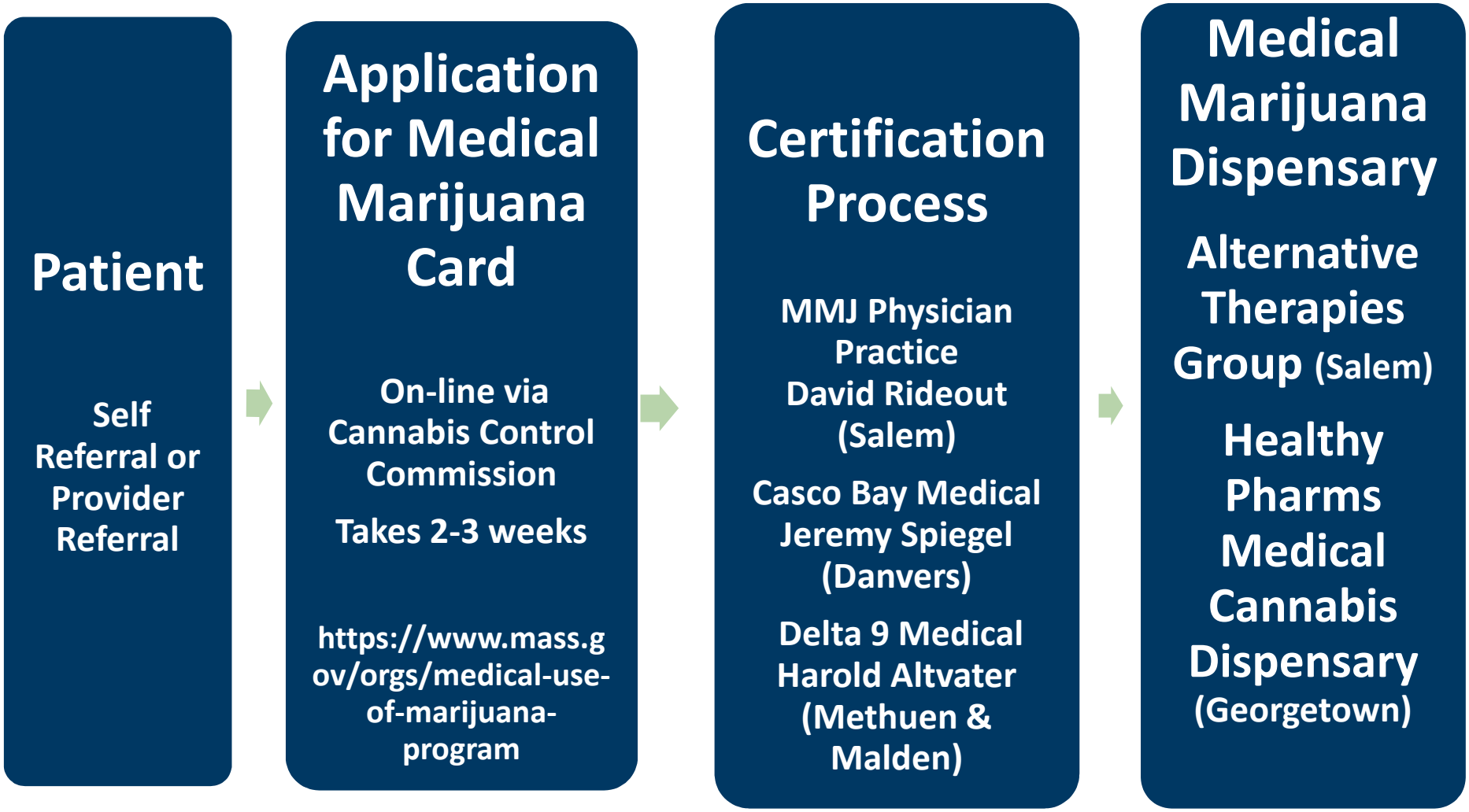
Medical Cannabis /Marijuana (MMJ)

Debilitating medical conditions:

Cancer	AIDS	glaucoma		HIV
Crohn's Dx	Hep C	ALS	PD	MS

*"**Debilitating**"* defined as causing weakness, cachexia, wasting syndrome, intractable pain, or nausea, or impairing strength or ability and progressing to such an extent that one or more of patient's major life activities is substantially limited.

Medical Cannabis Access Process



- ***As of January 2019: 49 RMDs (Registered Marijuana Dispensaries); 59,161 active patients & 288 registered providers***

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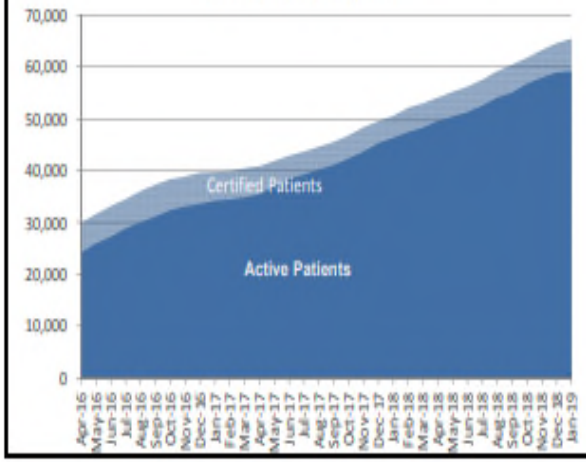
Massachusetts Medical Use of Marijuana Program: External Dashboard — Jan-19

REGISTRATION

Patient Count Snapshot

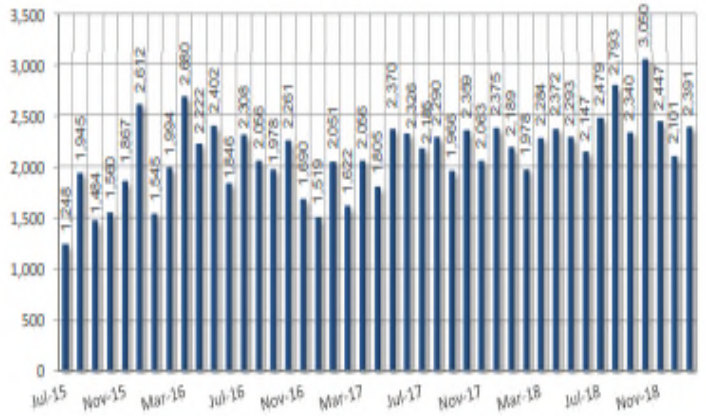


Patient and Caregiver Metrics	New in January	Total through January 31
Total Active Patient Certifications	2,740	65,423
Total Active* Patients	2,391	59,161
Total Active** Caregivers	364	7,039

* certified and registered
** registered

Certified Healthcare Providers Metrics	New in January	Total through January 31
Registered Physicians	5	244
Registered CNP	2	44

New Active* Patients

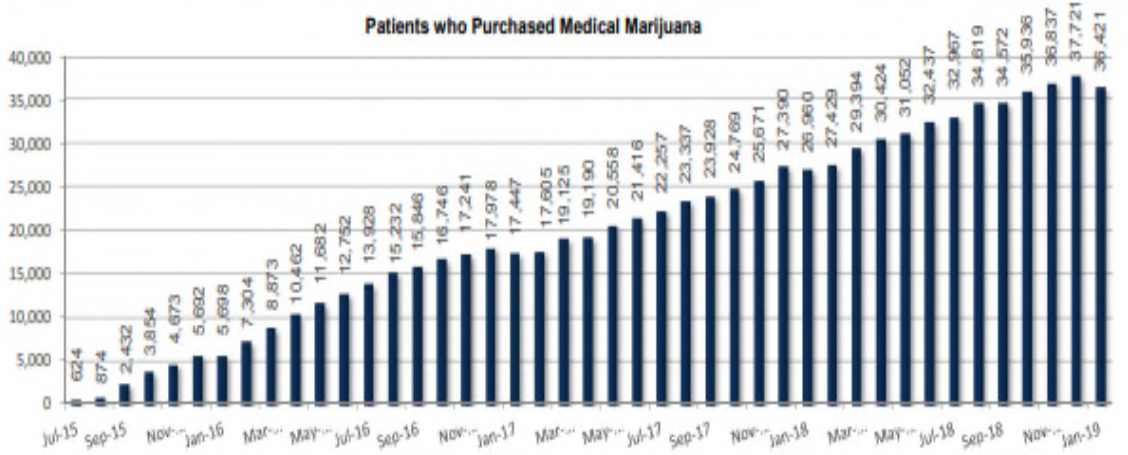


COMPLIANCE

Aggregate RMD Business Activity	New in January	FY Total through January 31
Unique Patients Served	36,421	59,860
Unique Caregivers Served	1,495	3,061
MMJ Sold, oz.	36,156	255,062

RMD Status	New in January	FY Total through January 31
RMDs With Final Certificate, approved to sell	0	49
RMDs with Final Certificate, not yet approved to sell	0	3
Expired Provisional Certificates	0	3
RMDs with Provisional Certificate, in Inspection Phase	0	103

Patients who Purchased Medical Marijuana



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Medical Cannabis Products

Flowers, Edibles, Capsules, Topicals, Tincture, Lozenges, Concentrates (vaping)

Flower | Edibles | Concentrates

Medical only

Brother Jonathan's White Chocolates: Sativa

Strain type: Sativa

Genetics: Gorilla Glue

Description: Brother Jonathan's Alchemy sativa white chocolates. Each package contains six servings. Each serving contains 10 mg of cannabis oil.

Cannabinoid Profile:

TAC: 72.54 mg D9-THC: 72.54 mg

Pricing: $30 each

Medical only

Brother Jonathan's White Chocolates: High CBD

Strain type: Hybrid

Genetics: Cannatonic

Description: Brother Jonathan's Alchemy indica High CBD chocolates. Each package contains six servings. Each serving contains 10 mg of cannabis oil.

Cannabinoid Profile:

TAC: 61.62 mg CBD: 46.02 mg
D9-THC: 15.6 mg

Pricing: $30 each

Medical only

Brother Jonathan's Capsules: Indica

Strain type: Indica

Genetics: White Rhino

Description: Brother Jonathan's Alchemy indica gelcap capsules. Each package contains 30 capsules. Each capsule contains 10 mg of cannabis oil.

Cannabinoid Profile:

TAC: 344.4 mg CBD: 27.9 mg
CBD-A: 0.9 mg THC-V: 1.8 mg
D9-THC: 302.4 mg CBC: 4.8 mg
CBN: 6.6 mg

Pricing: $50 each

Medi
onl

Brother Jonathan's Capsules: Sativa

Strain type: Sativa

Genetics: Gorilla Glue

Description: Brother Jonathan' Alchemy sativa gelcap capsule Each package contains 30 capsules. Each capsule contair 10mg of cannabis oil.

Cannabinoid Profile:

TAC: 294.3 mg CBD: 1.5 mg
THC-V: 2.1 mg D9-THC: 290.7

Pricing: $50 each

Consumable Cannabis Products





	Flower	Concentrate	Edible	Tincture*	Topical/Transdermal*
Consumption Method	Inhalation	Inhalation	Ingestion	Methods Vary Can be ingested or taken sublingually	Applied to Skin
Onset	Within 1 Minute	Within 1 Minute	30-120 Minutes	15-60+ Minutes Depending on consumption method	30-120 Minutes Dependent upon application location, additional ingredients, & other factors
Duration Depends on potency & individual metabolism	0.5 to 2 Hours	0.5 to 2 Hours	3+ Hours	1-4+ Hours Depends on consumption method and dose amount	1-4+ Hours Depends on application location, additional ingredients, & other factors (Could last as long as 72 hours)
Benefits	Easy to titrate dose	Less undesired plant material consumed	Discreet, no inhalation, longer-lasting effect	No inhalation, lasting effect, dose control	No ingestion, discreet, lasting effect, targeted relief, compatible w/ daily activities
Amount of Max THC	5-30%	40-90%	Typically 0-100 mg understanding serving size is crucial	Typically 0-100 mg understanding dosing is crucial	0-50 mg per application

***Clinical studies for these products are insubstantial. The figures above are estimated ranges based on the limited data available.**

MCR Labs Framingham MA accessed website February 21, 2019

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Edible Labeling

Each single serving must be marked, stamped, or imprinted with a symbol indicating it contains marijuana

Brownies with the printed THC stamp at the Zoots marijuana edibles production facility in Denver in 2016.
—*Bob Pearson / The Boston Globe*

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Gaps in MA Medical Cannabis Process

Physician “certifiers” NOT “prescribers”; no prescription

law requires “annual” recertification

Patient sent to dispensary:

Dispensary Agent, Compassion Care Technician, Patient Liaison or BUDTENDER

Inconsistent training; certification programs (4 hrs); some on-line (several modules); on-the-job training; some testing & exams

Dosing: Little or no guidelines; “Start low, go slow”

Delivery method determined by patient & budtender

RPh Dispenses: NY, Conn, PA, Minnesota & VA

U.S. Pharmacists' Role in Medical Cannabis Dispensing, by State

State	Pharmacists' Role in Dispensing
Mississippi	Cannabis may be legally acquired only through the National Center for Natural Products Research at the University of Mississippi and dispensed by the Department of Pharmacy Services at the University of Mississippi Medical Center
Wisconsin	Cannabis may be legally dispensed through physicians and pharmacies with an investigational drug permit from the FDA, unless the patient is qualified to access CBD from an out-of-state medical cannabis dispensary
Arkansas	Each cannabis dispensary is required to appoint a pharmacist consultant
Connecticut	Only pharmacists are allowed to apply for and obtain a cannabis dispensary license
Minnesota	Only pharmacists are permitted to give final approval for the distribution of medical cannabis to a patient
New York	A pharmacist is required to be on the premises to supervise the activities in a cannabis-dispensing facility whenever the facility is open or in operation
Pennsylvania	Primary cannabis-dispensing facilities are required to have a physician or pharmacist on-site whenever the facility is open to receive patients and caregivers

National Conference of State Legislatures. State medical marijuana laws. www.ncsl.org/research/health/state-medical-marijuanalaws.aspx. Accessed November 26, 2018.
National Community Pharmacists Association. State medical marijuana legislation and the pharmacist's role. www.ncpanet.org/advocacy/state-advocacy/medical-marijuana. Accessed November 26, 2018.

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Adverse Drug Events / Drug-drug Food-drug Interactions

ADEs:

psychosis hypertension

tachycardia hypertension hyperemesis syndrome

no respiratory depression *(no cannabinoid receptors in brain stem)*

Drug-drug Food-drug Interactions:

THC and CBD are primarily metabolized by Cytochrome P450 enzymes

- **Inhibitors** of these enzymes
  increase THC & CBD blood levels
- **Inducers** of these enzymes
  decrease THC & CBD blood levels

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Drug-Drug and Drug-Food Interactions

Cannabidiol (CBD)

Inhibitors Increase CBD Levels

Ritonavir
Verapamil
Voriconazole
Fluconazole
Omeprazole

Inducers Decrease CBD Levels

Carbamazepine
St. John's wort
Primidone
Rifampin

CBD Increases Substrates Below:

Amiodarone
Warfarin
Clopidogrel
Fenofibrate
Amitriptyline
Citalopram
Fluoxetine

Carbamazepine
Clobazam
Lamotrigine
Phenytoin
Valproic acid
morphine

CBD may Increase or Decrease Substrates

Amitriptyline
Bupropion
Cyclobenzaprine

CNS depressants (e.g. alcohol, opioids, benzodiazepines) → SE (e.g. dizziness, drowsiness)

High calorie / fat food → increases CBD absorption

Delta-9-tetrahdrocannabinol (THC)

Inhibitors Increases THC Levels

Sulfamethoxazole
Clarithromycin
Telithromycin
Voriconazole
Fluconazole
Ketoconazole
Grapefruit
Ritonavir
Indinavir
Viekira Pak
Verapamil
Conivaptan
PPIs
Ginko

Inducers Decrease THC Levels

Carbamazepine
Phenytoin
St John's Wort

Displaces highly protein bound drugs → higher drug levels, ADEs & toxicities

e.g. monitor & adjust dosing of cyclosporine & warfarin when starting or changing THC doses

THC may have additive effects with hypnotics, sedatives, psychotropics & alcohol

References: The Answer Page
Comparison of Cannabinoids Prescriber Letter Sept 2018

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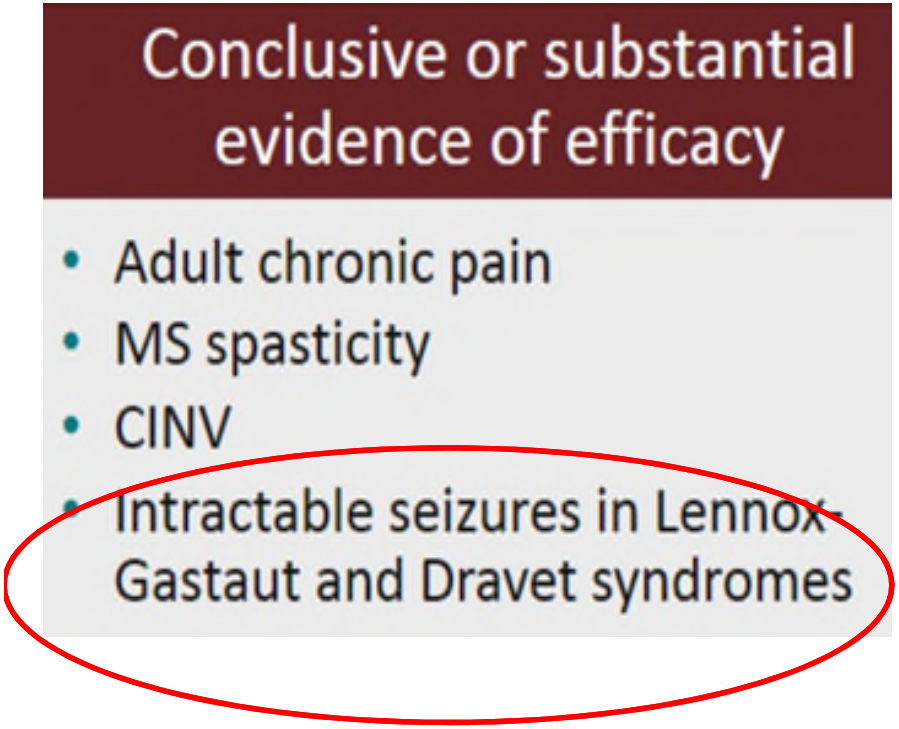
What is the evidence of efficacy?

Cannabis & Cannabinoids
Evidence of Efficacy
Conclusive

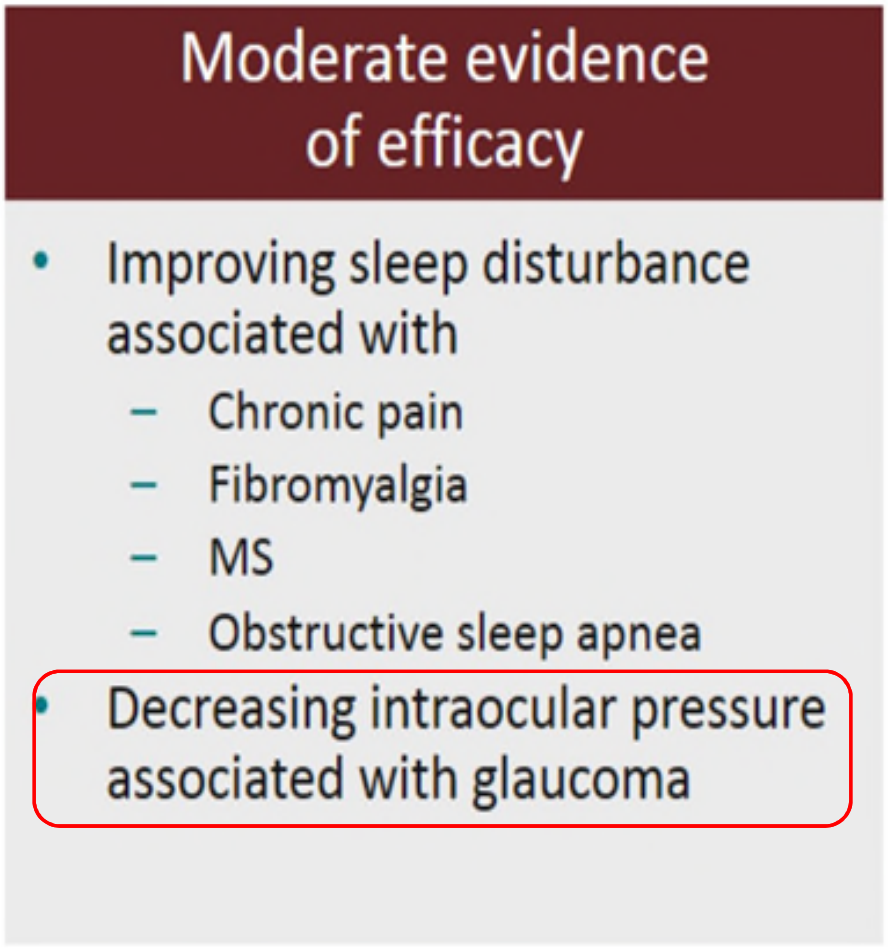


- Treatment **Chronic Pain** in Adults
- Antiemetics in treatment of **chemotherapy-induced nausea & vomiting (CINV)** (oral cannabinoids)
- Improving patient-reported **MS spasticity** symptoms (oral cannabinoids)

MacCallum CA, et. Eur J Intern Med. 2018;49:12-19

The Health Effects of Cannabis & Cannabinoids: Current State of Evidence & Recommendations for Research; National Academies of Sciences, Engineering, & Medicine January 2017

Evidence of Efficacy
Moderate

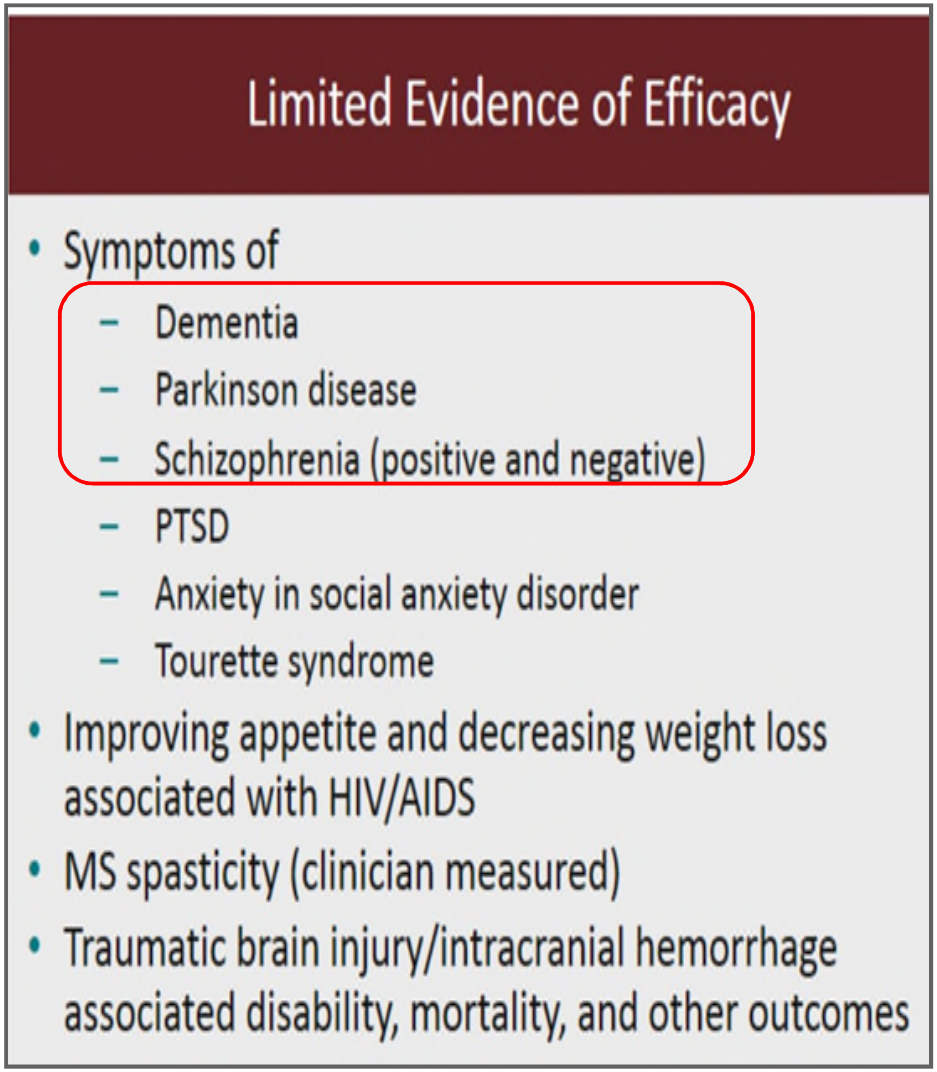


- Improving short-term sleep outcomes in sleep disturbance associated with
  - **obstructive sleep apnea**
  - **Fibromyalgia**
  - **Chronic pain**
  - **MS**

  (cannabinoids, primarily nabiximols)

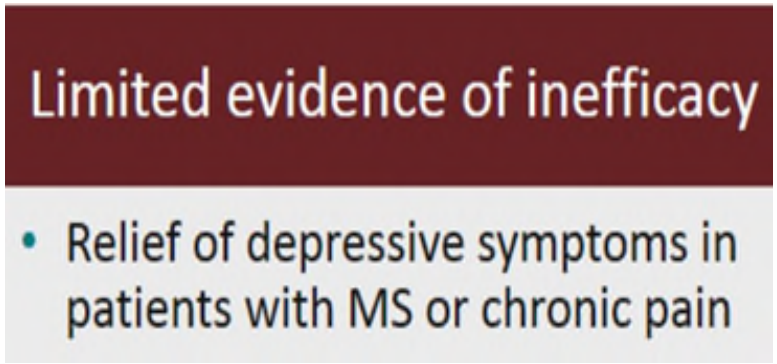
Evidence of Efficacy

Limited



- Increasing appetite & decreasing **weight loss associated w/ HIV/AIDS** (cannabis & oral cannabinoids)
- Improving clinician-measured **MS spasticity** symptoms (oral cannabinoids)
- Improving **symptoms of Tourette syndrome** (THC capsules)
- Improving **anxiety symptoms**, as assessed by public speaking test, in individuals with **social anxiety disorders** (cannabidiol)
- Improving **symptoms of PSTD** (nabilone 1 trial)
- Better outcomes (i.e. mortality, disability) after **a traumatic brain injury or intracranial hemorrhage**

Evidence of <u>Inefficacy</u>
Limited



- Dementia (cannabinoids)
- Intraocular pressure associated with glaucoma (cannabinoids)
- Depression symptoms in patients with chronic pain or MS (nabiximols, dronabinol and nabilone)

Evidence of Efficacy or Inefficacy

Insufficient

Insufficient evidence of efficacy or inefficacy

- Addiction abstinence
- Cancers, including glioma
- Cancer-associated anorexia, cachexia syndrome, and anorexia nervosa
- Symptoms of
  - Irritable bowel syndrome
  - Amyotrophic lateral sclerosis
  - Chorea and some neuropsychiatric associated with Huntington disease

- Cancers, including gliomas (cannabinoids)
- CA associated anorexia cachexia syndrome & anorexia nervosa (cannabinoids)
- IBS symptoms (dronabinol)
- Spasticity (pts w/ spinal cord injury (cannabinoids)
- ALS symptoms (cannabinoids)
- Chorea & certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids)
- PD motor symptoms or levodopa-induced dyskinesia (cannabinoids)
- Dystonia (nabilone & dronabinol)
- Mental health outcomes in pts with schizophrenia or schizophreniform psychosis (cannabidiol)

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Take Away

FDA approved products different from MMJ; state oversight

- Little or no regulation of on-line or street products

Patient Talking Points:

- Same approach to counseling as would for any other medications, including discussing risks associated w/impairment, safe storage, ADEs, DI & side-effects
- Encourage open dialogue
- Contraindicated in pregnancy & breastfeeding
- Discuss route of administration; onset varies (delayed)
- Assess for all OTC, (CAM) complementary alternative medications; herbals, cannabis, etc.

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Take Away

Provider Points:

- Conventional Therapy Ineffective for Specific Indication
- Assess Risk for Addiction; Informed Consent
- Check PMP

Cannabis use is a “polarizing topic”

Stigma associated with use

Don’t ask, don’t tell environment

More research needed; schedule status needs to change

Good Reference: The Health Effects of Cannabis & Cannabinoids: Current State of Evidence & Recommendations for Research; National Academies of Sciences, Engineering, & Medicine January 2017

CE Pharmacy Times - Demystifying Medical Cannabis
https://https://www.pharmacytimes.com/pressroom/pharmacy-times-continuing-education-to-launch-educational-video-activity-on-demystifying-medical-cannabis