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Medical Cannabis Program

Impact of Cannabis Use on Pain

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Disclaimer

- The opinions shared during this meeting do not necessarily reflect the position of the Medical Cannabis Program.
- The Medical Cannabis Program does not endorse any specific product, producer, or vendor.

Announcements

- Updates to Online Patient Portal
- Alert - Green Health Docs
- Updated References for High Potency
- Questions

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Pain Among Adults[1] - 2021

- An estimated 20.9% of U.S. adults (51.6 million persons) experienced chronic pain.

- 6.9% (17.1 million persons) experienced high-impact chronic pain.

Cost of Pain[2,3]

- Chronic pain contributes to an estimated ***$560 billion to $635 billion*** each year in direct medical costs, lost productivity, and disability programs.

- The cost of pain was more than that of heart disease and cancer treatments.

Opioid Crisis[4,5]

- Cost of fatal opioid disorder and fatal opioid overdose:
  - 2017 - $1.02 trillion
  - 2020 - $1.50 trillion

- Medical cannabis has gained traction as a tool in the fight against the opioid epidemic.

Why Cannabis?[6]

Positive Perceptions[7]

- Relatively safe profile
- Does not cause respiratory depression
- Seen as not addictive compared to opioids
- Actual pain relief
- Improved sleep

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Reported Use[8]

- In states with medical cannabis laws, 3 in 10 persons reported using cannabis to manage their pain.
- Of these, more than half of reported that use of cannabis led them to decrease use of prescription opioid, prescription nonopioid, and over-the-counter pain medications.
- Less than 1% reported that use of cannabis increased their use of such medications.

30 Qualifying Conditions

- *Alzheimer's Disease*
- Amyotrophic Lateral Sclerosis (ALS)
- *Anxiety Disorder*
- *Autism Spectrum Disorder*
- Cancer
- Crohn's Disease
- Damage to the Nervous Tissue of the Spinal Cord (with objective neurological indication of intractable spasticity)
- Epilepsy/Seizure Disorder
- *Friedreich's Ataxia*
- Glaucoma
- Hepatitis C Infection currently receiving antiviral therapy
- HIV/AIDS
- Hospice Care
- Huntington's disease
- Inclusion Body Myositis
- Inflammatory Autoimmune-mediated Arthritis
- *Insomnia*
- Intractable Nausea/Vomiting
- *Lewy Body Disease*
- Multiple Sclerosis
- Obstructive Sleep Apnea
- *Opioid Use Disorder*
- Painful Peripheral Neuropathy
- Parkinson's disease
- Post-Traumatic Stress Disorder
- Severe Anorexia/Cachexia
- Severe Chronic Pain
- Spasmodic Torticollis (Cervical Dystonia)
- *Spinal Muscular Atrophy*
- Ulcerative Colitis

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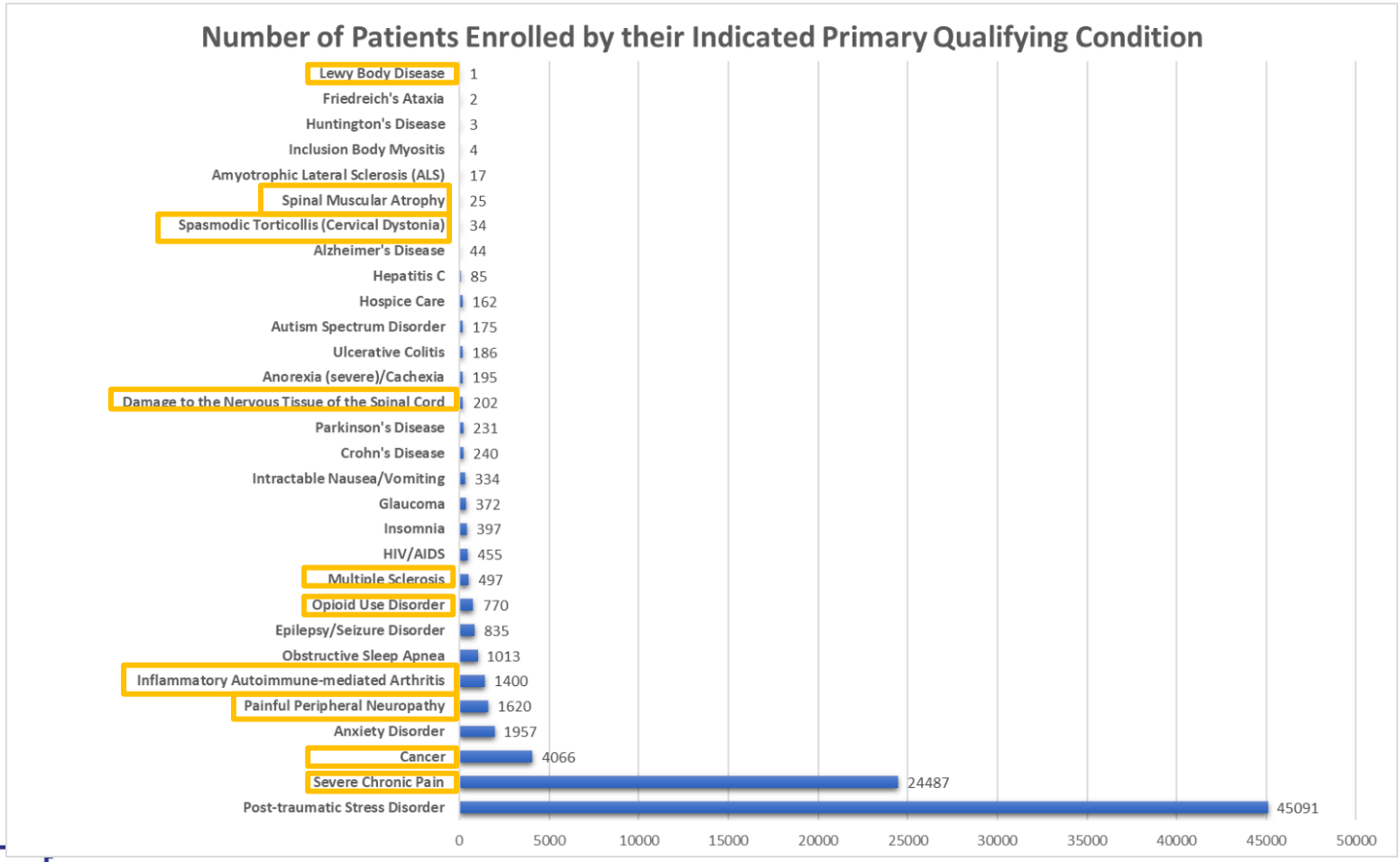
Demographics – November 2023

Number of Patients Enrolled by their Indicated Primary Qualifying Condition

Alzheimer's Disease	44	Inclusion Body Myositis	4
Amyotrophic Lateral Sclerosis (ALS)	17	Inflammatory Autoimmune-mediated Arthritis	1,400
Anorexia (severe)/Cachexia	195	Insomnia	397
Anxiety Disorder	1,957	Intractable Nausea/Vomiting	334
Autism Spectrum Disorder	175	Lewy Body Disease	1
Cancer	4,066	Multiple Sclerosis	497
Crohn's Disease	240	Obstructive Sleep Apnea	1,013
Damage to the Nervous Tissue of the Spinal Cord	202	Opioid Use Disorder	770
Epilepsy/Seizure Disorder	835	Painful Peripheral Neuropathy	1,620
Friedreich's Ataxia	2	Parkinson's Disease	231
Glaucoma	372	Post-traumatic Stress Disorder	45,091
Hepatitis C	85	Severe Chronic Pain	24,487
HIV/AIDS	455	Spasmodic Torticollis (Cervical Dystonia)	34
Hospice Care	162	Spinal Muscular Atrophy	25
Huntington's Disease	3	Ulcerative Colitis	186

Demographics – November 2023



CANNABIS PUBLIC POLICY CONSULTING

Variable	%Endorsed
What health conditions or symptoms have you used cannabis for that a medical provider did NOT recommend?	
Pain	21
Nausea or appetite stimulation	21
Anxiety and/or depression	21
Sleep disorders	17
Replacing other substances (e.g., opiates, alcohol)	10
Gastrointestinal issues	7
Autism	3
ADHD	3
Total number of non-recommended conditions treating with cannabis	
Zero	31
One	55
Two	7
Three	3
Four or more	3

CANNABIS PUBLIC POLICY CONSULTING

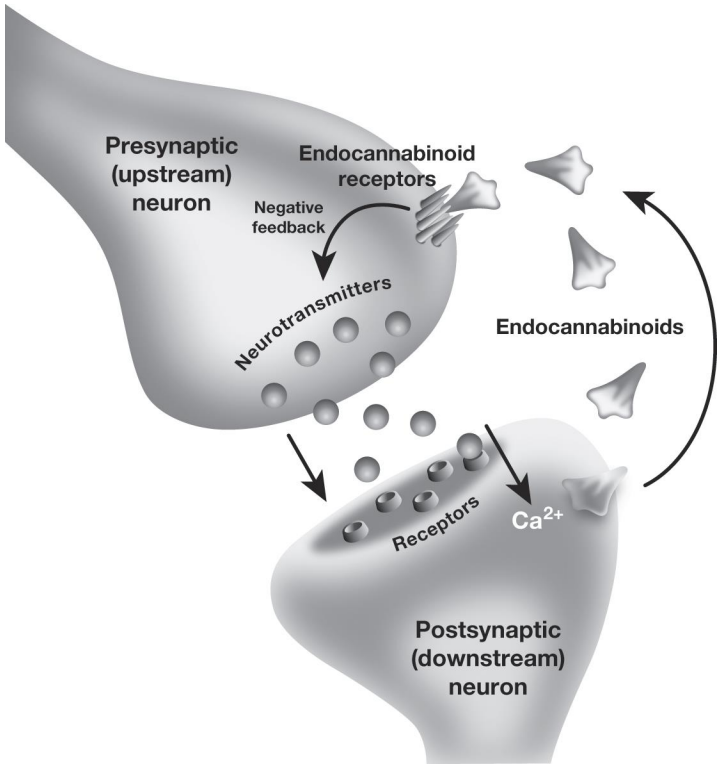
Variable	%Endorsed
Do you plan to use specific treatment methods (i.e., specific products for specific conditions or symptoms)?	
No	24
Yes	76
Identification of specific treatment methods by condition/symptom	
Pain	
Concentrate	21
Edible	17
Flower	17
Topical	17
CBD	3
Anxiety and/or Depression	
Concentrate	14
Edible	10
Flower	28
PTSD	
Concentrate	10
Edible	14
Flower	24
Sleep / Insomnia	10
Edible	14
Flower	
Replace opioids	
Flower	3
Replace alcohol	
Flower	3
Appetite stimulation / Nausea	
Flower	7
Crohn's Disease	
Edible	3
Autism Spectrum Disorder	
Flower	3
Edible	3
Epilepsy	
Flower	3

Endocannabinoid system (ECS)

- The ECS is comprised of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the enzymes responsible for the synthesis and degradation of the endocannabinoids.
- It is distributed throughout the central and peripheral nervous system and affects biological functions—including eating, anxiety, learning and memory, reproduction, metabolism, growth and development—via an array of actions throughout the nervous system.
- Goal is to help maintain homeostasis.

How does the ECS Function?[9]

- Negative Feedback Loop.
- Decreases the output of the system in order to stabilize that system.



Endocannabinoids

- Anandamide (AEA) – 1992
  - “Bliss molecule” - stimulates a sense of happiness
  - CB1/CB2 agonist
  - TRPV1 agonist
  - Degradation in the CNS by fatty acid amino hydrolase (FAAH)

- 2 – Arachidonyglycerol (2–AG) – 1995
  - Most abundant endocannabinoid
  - Full agonist at CB1 and CB2 Receptors
  - GPR55 agonist
  - Degradation by monoacyglycerol lipase (MAGL), cyclooxyngenase-2 (COX-2)

Cannabinoid Receptors

- CB1
- CB2
- TRPV1
- GPR55

CB1[10,11]

- Psychoactive and antiemetics effects
- Primary site for AEA (and THC)
- CB1 receptors are GPCRs (G protein-coupled receptor)
- Most abundant GPCR in the central nervous system
- Expressed in presynaptic terminals throughout the CNS and act to inhibit neurotransmitter release
- Additionally found in – (Gastrointestinal System, Adipocytes, Liver Tissue, Skeletal Muscle)
- CB1 receptors are indicated in many disorders that impact the CNS including several neurodegenerative disorders such as Huntington's disease (HD), multiple sclerosis (MS) and AD

CB2[11,12]

- CB2 receptors are GPCRs (G protein-coupled receptor)
- Expressed in the periphery, primarily immune cells, but evidence now indicates they are also expressed in CNS.
- Activation results in inhibition of neuroinflammatory signaling pathways by altering cytokine profiles.
  - Reduces pro-inflammatory factors
  - Increases the concentration of anti-inflammatory factors
- CB2 agonists promote the clearance of amyloid plaques and recovery of the neuronal synaptic plasticity in setting of Alzheimer's disease
- In setting of chronic opioid administration
  - Mitigated development of opioid tolerance, opioid-induced reward mechanisms
  - Restored the analgesic efficacy of opioids

TRPV1 (Transient Receptor Potential Vanilloid 1)[13,14]

- Non-selective cation channels gated by capsaicin, protons and heat that promote neuronal excitability.
  - Expressed in both peripheral and central pain pathways
  - AEA is a full agonist
  - Activated by CBD
- Activation in sensory neurons mediates nociception in the ascending pain pathway.
- Activation involving RVM and PAG mediates antinociception in the central descending pain pathway, especially in the presence of inflammation and neuropathic pain.
- Activation also causes release of neuropeptides from peripheral and central nerve terminals including the vagal terminal innervating the gut.

GPR55 (CB3)[15]

- G coupled receptor
- Signaling distinct from CB1 and CB2
- Highly expressed in large dorsal root ganglion neurons, adipose tissue, and microvascular endothelial cells
- Activated by AEA and THC
- Releases calcium from intracellular stores leading to enhanced neuronal excitability
- Inhibits M-Type Potassium Current

Phytocannabinoids

- Phytocannabinoids are naturally occurring plant molecules that interact with cannabinoid receptors.
- THC (^-9-Tetrahydrocannabinol) and CBD (Cannabinol) are usually the most abundant cannabinoids in Cannabis plants and are also the most studied cannabinoids.

THC (^-9-Tetrahydrocannabinol)

- Psychoactive
  - modulation of glutamate and GABA
- Regulated
- “Cannabis”
- Partial agonist at CB1 > CB2
  - primary mechanism of action
- GPR55 agonist
- Helps with:
  - Pain
  - Nausea

THC – pain[16]

- Reduces NMDA (N-methyl-D-aspartate) responses resulting in anesthesia and memory deficits
- Blocks capsaicin-induced hyperalgesia
- Inhibits CGRP (Calcitonin Gene-Related Peptide) activity
- Increases cerebral serotonin production
- Agonist at PPAR (Peroxisome proliferator-activated receptor agonist) inhibiting inflammation and oxidative stress
- Enhances analgesia from Kappa opioid receptor agonists
- Stimulates production of beta-endorphins
- Increases proenkephalin mRNA levels in brainstem regions involved in pain processing
- Produces analgesia similar to opioids when administered intraventricularly/intrathecally

THC – pain[17]

- Analgesic effects of THC in chronic neuropathic pain in humans have been shown to occur at plasma levels well below those associated with euphoria.
- Patient may not need to experience the psychotropic effects of THC to achieve pain relief.

CBD (Cannabinol)

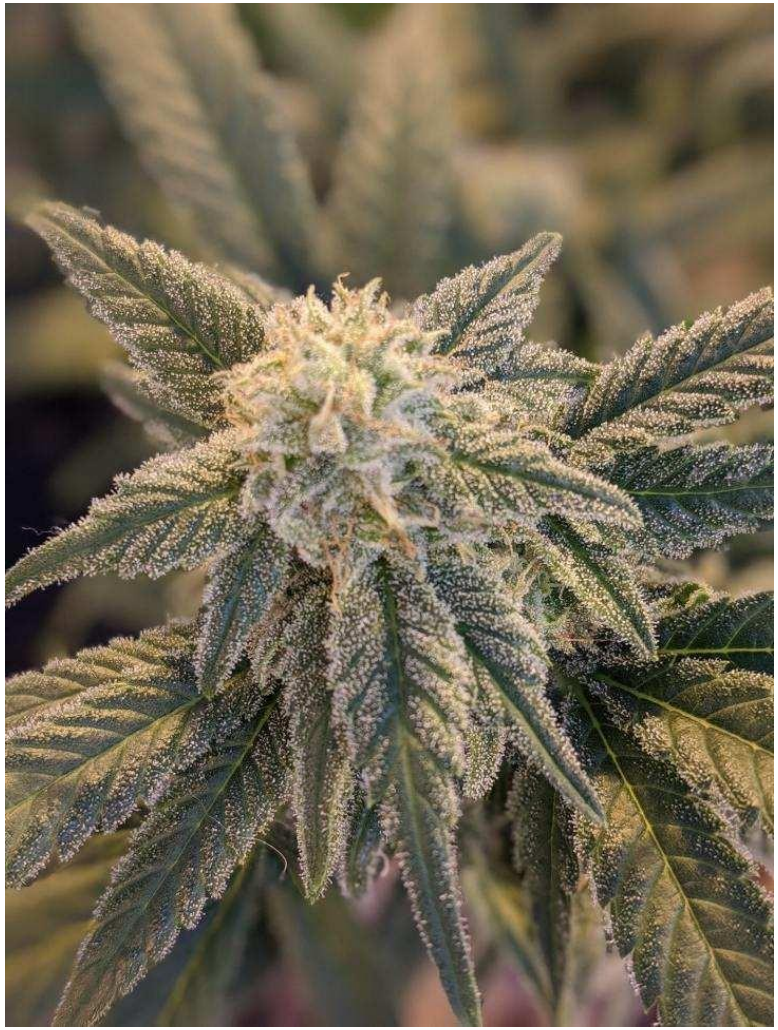
- Non-psychoactive
- Not regulated
- "Hemp"
- Negative allosteric modulator at CB1 and CB2 receptors
  - Can act as an antagonist at CB1 & CB2 receptors in the presence of THC thereby reducing the effects of cannabis intoxication
- GPR55 antagonist
- TRPV1 agonist
- Helps with:
  - Inflammation
  - Seizures

CBD – pain[16]

- inhibits AEA uptake and metabolism
- a positive allosteric modulator at α1 and α1β glycine receptors
- acts as a μ opioid receptor ligand and a positive allosteric modulator at μ and δ opioid receptors
- powerful analgesic and anti-inflammatory effects mediated by both cyclooxygenase and lipoxygenase inhibition
- Agonist at PPAR (Peroxisome proliferator-activated receptor agonist) inhibiting inflammation and oxidative stress
- Suppresses degradation of 5HT precursor tryptophan
- Inhibits anandamide breakdown by FAAH

540 distinct chemical compounds

- More than 113 different phytocannabinoids[18]
- More than 200 terpenes – (aromatic compounds)[19]
- More than 20 Flavonoids – (color producers)[20]



Entourage Effect

- The mechanism by which cannabis compounds act synergistically to modulate the overall effects of the plant.
- Estimated to be over 1,000 different strains of cannabis each with its own special ratio of compounds.
- Limitless options for potential treatments, but hard to predict, replicate, or study.
- Not addressed in most studies

News

- On August 29, 2023, the Department of Health and Human Services (HHS) recommended to the Drug Enforcement Agency (DEA) that cannabis be rescheduled from Schedule I to Schedule III under the Controlled Substances Act (CSA).

    - Schedule III – Tylenol with codeine, ketamine, suboxone, anabolic steroids, and testosterone.

DEA enforces drug laws – FDA enforces drug standards

Prescriptions Cannabinoids

- Cesamet (nabilone) - *available in U.S.*
  - Synthetic cannabinoid similar to THC
  - Nausea associated with cancer chemotherapy
- Marinol (dronabinol) - *available in U.S.*
  - Synthetic THC
  - Anorexia and weight loss
  - Nausea and vomiting in cancer chemotherapy
- Epidiolex (cannabidiol) - *available in the U.S.*
  - Plant-derived CBD
  - Specific pediatric seizures – DS, LG, tuberous sclerosis
- Sativex (nabiximols) - ***not*** *available in U.S*.
  - Two cannabis extracts in 1:1 ratio
    - Tetranabinex = high THC/Nabidiolex = high CBD
  - MS-related spasticity

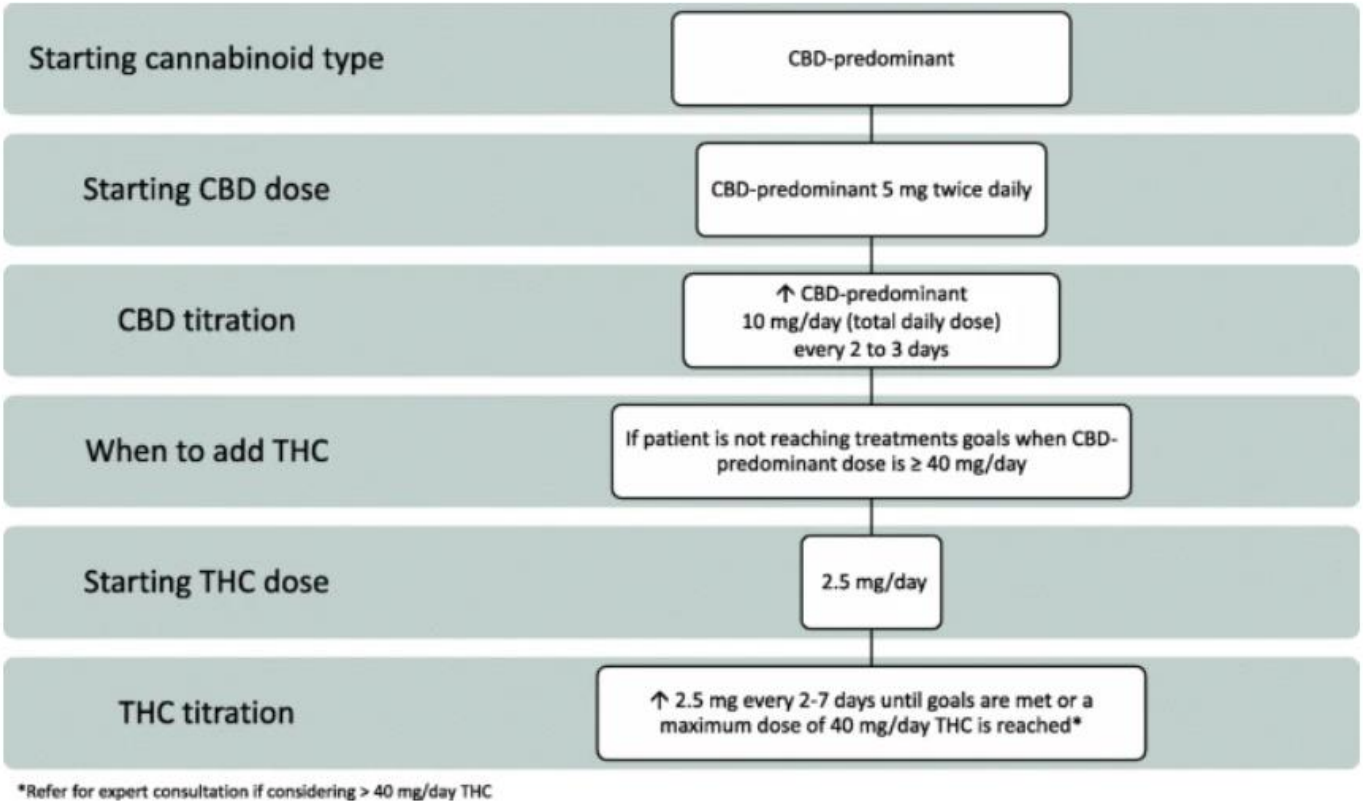
Ensuring a good outcome[21]

- Thorough history and physical exam
  - Determine appropriate therapy
- Monitor symptomatic improvement
  - Routine follow-up
  - Questionnaires
- Collaboration amongst treatment providers
  - physiatrist, physical therapist, psychologists, pain management physicians, neurologists, psychiatrists, and social workers

Dosing and administration[22]

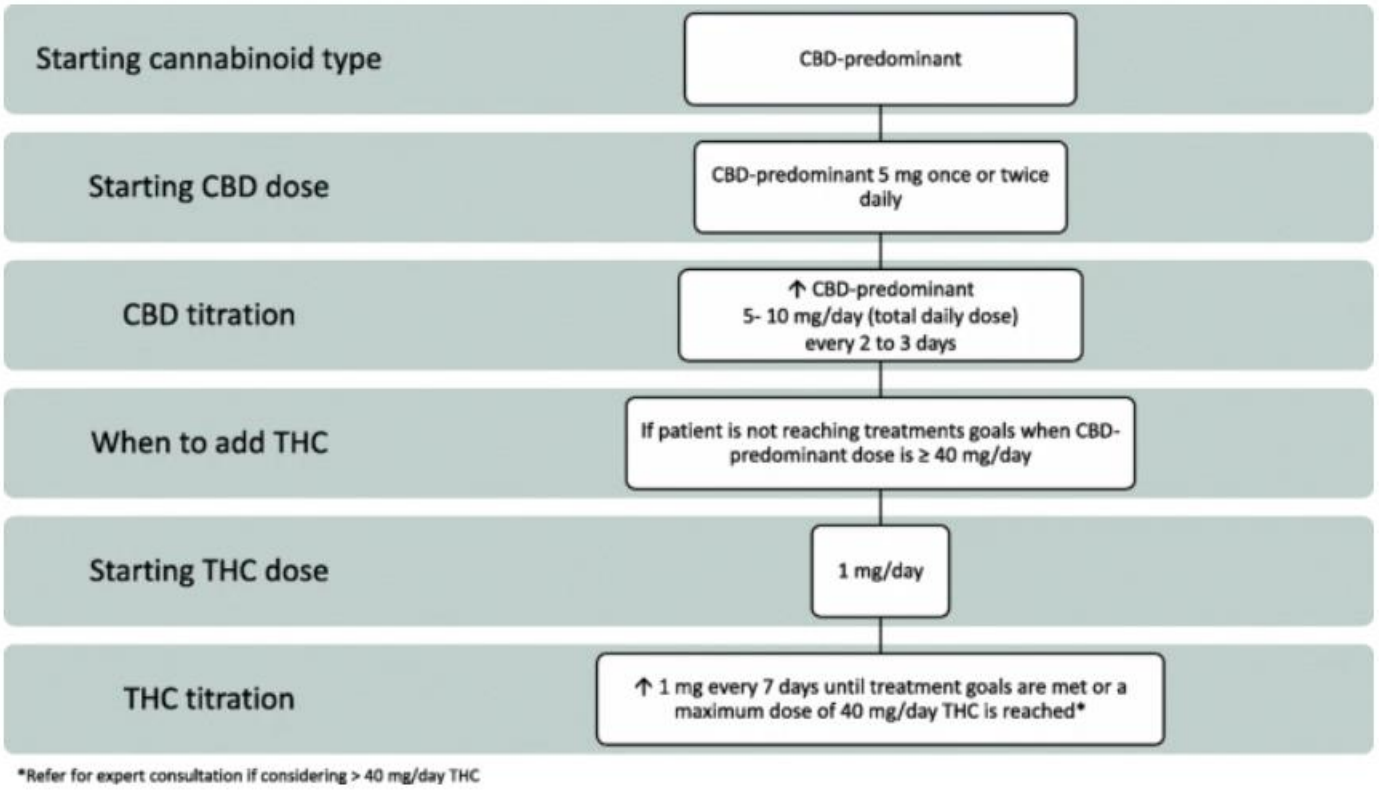
- There have also been a few randomized controlled trials studying the dosing and administration of medicinal cannabis. In one specific study, experts across nine different countries developed three different treatment protocols for the dosing and administration of cannabis when treating patients with chronic pain.

Routine protocol[22]



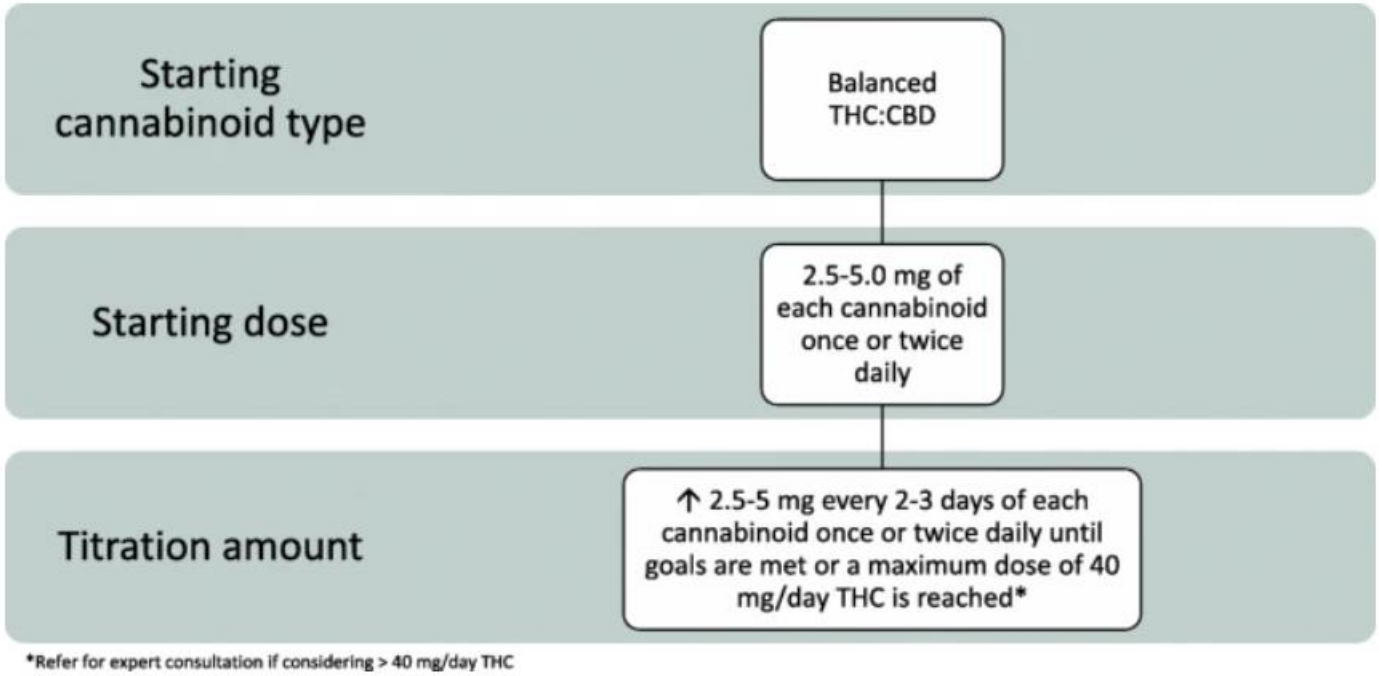
Routine protocol for medical cannabis dosing and administration

Conservative protocol[22]



Conservative protocol for medical cannabis dosing and administration

Rapid protocol[22]



Rapid protocol for medical cannabis dosing and administration

Which strains[23]

- Indica strains have historically been considered best for treating chronic pain.
  - Moderate CBD
  - High THC
  - High terpenes
- High CBD strains also seen as beneficial.
- Old “indica” and “sativa” distinctions are not necessarily accurate - many sativa varieties may be equally as effective – everything is a hybrid!

Examples of possible strains

- ACDC
- Harlequin
- Cannatonic
- Northern Lights
- White Widow
- Blueberry

Which Terpenes[24,25,26,27]

- Myrcene
- Pinene
- Linalool
- Limonene
- Humulene
- Caryophyllene

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Which ratio

- Mild Pain – Consider a CBD:THC ratio of 20:1 or 10:1.
- Neuropathic Pain – A balanced ratio of CBD:THC 1:1.
- Severe Pain – More potent ratio of CBD:THC 1:10 or 1:20*.

*high potency/concentrate range

What do we know about high potency products?

- Cannabis products are not standardized.
- Potency of THC can vary widely.
- Consumers knowledge of THC levels in the products they use is low.
- Concentrates are more likely to contain residues and contaminants.
- New concentrates continue to flood the market.

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Dangers of High Potency

- Young people are more vulnerable
  - socially and developmentally
- Accidental overconsumption
- Rapidly develop tolerance
- Using high THC products increases the risk of developing of Cannabis Use Disorder.
- Increased likelihood of Cannabis Withdrawal
- Cannabis Hyperemesis Syndrome
- Potential lifelong mental health issues - psychosis

Contraindications/Cautions

- Pregnant, planning to conceive, or breastfeeding women
- People with psychiatric disorders
  - Schizophrenia
  - Bipolar Disorder
  - Suicidality
- Age less than 25 years old
- People with pre-existing addiction disorders
- Chronic lung disease (smoked cannabis)
- Chronic heart disease
- Reduced drug elimination mechanisms (hepatic or renal)
- People with potential adverse drug interactions

Cannabis and surgery[28]

- November 2020 - American Society of Regional Anesthesia and Pain Medicine released guidelines on cannabis use in relation to surgery.
- Recommended that all patients undergoing procedures requiring anesthesia should be asked about cannabis use.
- Noted that regular use may worsen pain and nausea after surgery and increase the need for opioids.

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Any questions?

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THANK YOU!!