Clinical Evidence for Medical Marijuana

Marijuana is made up of many different components, and the composition of each strain is different. This makes clinical efficacy and predicting side-effects challenging. Evidence quantity and quality differs for each disease state, so it's possible to find both supporting and opposing literature for each disease state, thus careful review is necessary

Providers should make sure they're comfortable with the certification process if they choose to certify a patient for medical marijuana use. Marijuana is federally a Schedule I controlled substance, and not covered by insurance, so the cost or financial burden should be considered during discussions with patients.

The table below lists the level of evidence for benefit for each of the symptoms and disease states listed:

Symptom/Condition	Evidence of Benefit
Nausea/vomiting	Low
Appetite stimulation	Low/Moderate
Glaucoma	Low
Epilepsy	Whole plant – Low/Moderate CBD - High
Pain management	High
PTSD	Short term, as-needed use – Moderate/High Daily/chronic use – Low (may cause harm)
Crohn's Disease	Moderate
Multiple Sclerosis	Pain and spasticity – High Other symptoms – Low

What is marijuana? [1-3]

- Marijuana is a plant-based psychoactive substance that is generally derived from one of two plants – Cannabis sativa or Cannabis indica
- There are approximately 113 cannabinoids found in the marijuana plant. The two most common are tetrahydrocannabinol (THC) and cannabidiol (CBD)
- THC is the most common cannabinoid in marijuana and is responsible for the psychoactive effects of the substance
- CBD is the second most common cannabinoid in marijuana and appears to be responsible for most of the medical benefit. Additionally, CBD can down-regulate the psychoactive effects of THC
- Cannabinoids act on our endocannabinoid system by targeting CB1 receptors (primarily in the brain/central nervous system) and CB2 receptors (primarily found in peripheral organs and immune cells)

How is marijuana used? [1-4]

- The most common methods of marijuana administration are smoking/vaping, edibles, and topical products
- Smoking/vaping produces effects within seconds to minutes. Peak effects occur within 30 minutes and can last for 1-3 hours depending on amount used. "Dabbing" is a form of smoking and involves vaporization of high THC content hash oils
- Edibles have variable effects based on bioavailability. Bioavailability can range from 20-40%, even within the same batch. Onset of effects can take 30-120 minutes with peak effects occurring after 2-4 hours. Duration of effects is approximately 5-8 hours depending on amount used
- Topical products are potentially beneficial for local effects only. The size of the cannabinoids limits systemic exposure. Most benefit appears to be from application technique (e.g. rubbing in a lotion for muscle aches)
- Doses required for effect are variable and dependent on method of use, product potency, and target symptom. In general doses between 5-25 mg of THC and 10-200 mg of CBD are seen in most studies. Treatment should start with lowest dose and be titrated as needed to effect assuming the same route of use and product.

Can marijuana effect other medications? [5-8]

- THC has metabolism inhibition properties and can increase levels of medications metabolized by CYP 1A2, 1B1, 2B6, 2C9, 2C19, 2D6, and 2J2. Degree of inhibition depends on the potency of THC in the product and amount used. This includes medications such as clozapine (1A2), methadone (2B6, 2C19), warfarin (2C9), and most beta blockers (2D6)
- CBD has metabolism inhibition properties and can increase levels of medications metabolized by CYP 1A2, 1B1, 2C9, and 3A4/5/7. Degree of inhibition depends on the potency of CBD in the product and amount used. In addition to examples provided above, this also includes many other medications such as numerous antiepileptic agents and DOACs (3A4)
- Smoking (i.e. burned hydrocarbon) can induce CYP 1A2, thus decreasing levels of medications metabolized by this pathway. Induction of this pathway normally overcomes the inhibition by the cannabinoids. An exception to this is dabbing due to the concentration of THC in those products
- More information regarding substrate, inhibition, and induction properties of medications can be found in the Flockhart Table published by Indiana University. It does not include cannabinoids at this time
- The exact degree of inhibition for different cannabinoids is not well known. There exist contradictory studies for some enzymes and only in vitro data for some other enzymes. This area of study will evolve as marijuana use increases. Caution should be used when combining marijuana with products that have a narrow therapeutic index or in complex/hard to control patients

What are the common side effects of marijuana use? [2-4]

- Common side effects of marijuana use include sedation, altered senses, dissociation, challenges in problem solving, memory impairment, and tachycardia
- Hallucinations and delusions can occur with high dose marijuana use, especially THC
- Withdrawal from marijuana is uncommon, though people who use chronically may experience some withdrawal effects for a few days after use
- Withdrawal effects can include anhedonia, cyclic vomiting, headaches, cravings, appetite suppression, and fatigue. Residual hallucinations are possible with high-dose use

Are there any absolute contraindications to marijuana use? [9-12]

- Currently, due to the Schedule 1 nature of the substance, there are no true contraindications to use other than hypersensitivity to cannabinoids
- The only contraindication (other than hypersensitivity) listed in any of the FDA-approved cannabinoid products is with dronabinol solution and disulfiram use secondary to the alcohol content of the solution. This is not relevant to medical marijuana products
- Additionally, there is an allergy warning with cannabidiol and dronabinol due to the sesame seed oil suspending agent used
- It is plausible that inhaled marijuana products be avoided in patients with severe respiratory disease

What is the preliminary list of conditions for medical marijuana in South Dakota? [13-14]

- Acquired immune deficiency syndrome (AIDS) and positive status for human immunodeficiency virus (HIV)
    - Used for appetite stimulation, nausea, and pain
- Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease
    - Used for muscle spasms, pain, and appetite stimulation
- Multiple sclerosis (MS)
- Cancer associated with severe or chronic pain, nausea or severe vomiting, or cachexia or severe wasting
- Crohn's disease
- Epilepsy and seizures
- Glaucoma
- Post-Traumatic Stress Disorder (PTSD)

Antiemetic Efficacy [15-19]

- Clinical trials with nausea in cancer patients are mixed, though most studies demonstrate a lack of robust efficacy
- No well-powered studies exist comparing marijuana to traditional antiemetics used (e.g. 5HT3 antagonists, olanzapine)
- 2017 American Society of Clinical Oncology Antiemetic guidelines state evidence remains insufficient to recommend marijuana for prevention or treatment
- Overall evidence of benefit is LOW

Appetite Stimulation [20-25]

- Some smaller, older studies show benefit
- Anecdotally, a side effect of marijuana is "the munchies" where people report an increase in hunger and snacking after marijuana use
- An active control study with megestrol demonstrated inferior performance of marijuana
- A 2006 study demonstrated no benefit with oral cannabis
- Though people may temporarily increase intake, there appears to be no effect on weight and long-term outcomes
- Two FDA-approved products (dronabinol and nabilone) have robust efficacy. There is no demonstrated benefit of marijuana in patients who have failed these products
- Overall evidence of benefit is LOW/MODERATE

Glaucoma [26-28]

- Agonism of CB1 receptors in the eye can open the Canal of Schlemm and decrease intraocular pressure (IOP)
- A commonly cited 1980 study demonstrated a drop in IOP from 28 mmHg to 22 mmHg, though this is still above normal IOP
- Duration of effect is only approximately 3.5 hours, necessitating 6-8 times per day dosing
- Overall evidence of benefit is LOW

Epilepsy [29-35]

- Multiple studies demonstrate a decrease in seizure frequency with CBD administration. This is true in both children and adults
- An FDA-approved product (cannabidiol) is approved for adjunct treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet Syndrome, and Tuberous Sclerosis Complex (TSC)
- Whole-plant marijuana studies do not demonstrate the same clinical benefit, though high-CBD containing strains appear to be slightly more efficacious than high-THC strains
- Overall evidence of benefit for whole plant marijuana is LOW/MODERATE
- Overall evidence of benefit of CBD is HIGH

Analgesia [36-46]

- Agonism of CB1 receptors in the CNS and CB1/CB2 receptors in peripheral tissues creates analgesia
- Multiple studies show efficacy with whole plant marijuana, THC, and CBD administration
- A dose-finding study equated approximately 10 mg of THC with 60 mg of codeine
- Another study showed marijuana synergy with morphine SR, though this same synergy did not occur with oxycodone XR for unknown reasons
- Efficacy has been shown with both musculoskeletal pain and neuropathic pain, including HIV-induced neuropathy
- Overall evidence of benefit is HIGH

PTSD [47-52]

- Agonism of CB1 receptors in the CNS produces downregulation of the hypothalamic-pituitary-adrenal (HPA) axis, thus producing a decrease in release of catecholamines and cortisol
- With infrequent, short term use, this can produce anxiety relief
- Multiple studies that are shorter than three months in duration correlate as-needed marijuana use to decreases in anxiety scores in PTSD patients
- Since cortisol provides negative feedback for the HPA axis, chronic inhibition of cortisol release can strengthen the HPA axis and increase anxiety
- Long term studies in PTSD show worsening of PTSD symptoms and an increase in violent behavior and substance misuse with chronic marijuana use
- Overall evidence of short term, as-needed use is MODERATE/HIGH
- Overall evidence of daily chronic use is LOW (and may cause harm)

Crohn's Disease [53-56]

- Many studies demonstrate benefit with pain and nausea relief
- A white paper from the Crohn's and Colitis Foundation (CCF) highlights improvement in symptoms and quality of life per patient report, though also notes no disease-modifying benefit confirmed on endoscopy
- CCF's position statement supports policy changes that advances research, but calls the evidence "conflicting"
- Overall evidence of benefit is MODERATE

Multiple Sclerosis [57-59]

- Multiple studies demonstrate benefit with pain, muscle spasms, and spasticity symptoms
- A systematic review of 11 systematic reviews confirms this finding
- Evidence for smoking marijuana is lower than with edibles
- Evidence for non-pain or spasticity symptoms is lacking
- Overall evidence of benefit in pain/spasticity is HIGH
- Overall evidence of benefit in other symptoms is LOW

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