

The background features abstract, overlapping geometric shapes in various shades of purple and blue, creating a modern and professional aesthetic. The shapes are primarily triangles and polygons, some with thin white outlines, set against a light lavender background.

# Introduction to Clinical Cannabis Practice

by Deborah Malka MD, PhD

# What is a Cannabis Clinician Specialist?



# Cannabis Clinician Specialist

## What you need to know

- ▶ 1. Evaluate and diagnose medical conditions and medical history documents
- ▶ 2. Good clinical skills - perform an appropriate exam for the diagnosis
- ▶ 3. Good patient rapport - put patients at ease and counsel about treatment
- ▶ 4. Medical documentation skills - document history, physical and plan
- ▶ 5. Referral sources for medical and ongoing care
- ▶ 6. Expertise in the clinical use of medical cannabis - advise patients on the use, benefits and risks of cannabis for their condition

# Expertise in Clinical Cannabis

- ▶ 1. Basic science of cannabis chemistry, the endocannabinoid system, and other components of the plant
- ▶ 2. Effects of cannabis on body physiology, organs and systems
- ▶ 3. Properties of *Cannabis Sativa* as a medicinal herb vs. a pharmaceutical medicine
- ▶ 4. Qualifying medical conditions for the use of cannabis
- ▶ 5. State laws and decisions that affect the use of cannabis
- ▶ 6. Dosing suggestions and when to use the different routes of delivery
- ▶ 7. Effects of cannabis consumption at chronic and acute usage - tolerance, overuse, the withdrawal syndrome
- ▶ 8. CMEs, research and other informative sources to learn more

# Guidelines for a Missouri Certification

- ▶ Patients need the Physician Certification Form completed by an MD or DO - annual
- ▶ The physician must meet with and examine the qualifying patient and review the patient's medical records or medical history
- ▶ The physician must have a conversation with the patient about current symptoms, and risks associated with medical marijuana, including any known contraindications applicable to the patient
- ▶ The physician must create a medical record for the patient
- ▶ Certification is for a standard recommended dose of up to 4 ounces per month (for more than 4 ounces must submit two Alternative Physician Certification Forms)
- ▶ Minors under the age of 18 also need to submit a Parent/Legal Guardian Consent Form
- ▶ A qualifying patient or primary caregiver may cultivate cannabis plants - 6 flowering plants, 6 nonflowering plants, and 6 clones (plants under 14 inches tall) are allowed

# Qualifying Conditions in Missouri

- ▶ Cancer
- ▶ Epilepsy
- ▶ Glaucoma
- ▶ Intractable migraines unresponsive to other treatment
- ▶ A chronic medical condition that causes severe, persistent pain or persistent muscle spasms, including but not limited to those associated with MS, seizures, Parkinson's disease, and Tourette's syndrome
- ▶ Debilitating psychiatric disorders, including, but not limited to, post-traumatic stress disorder, if diagnosed by a state licensed psychiatrist
- ▶ HIV or AIDS
- ▶ A chronic medical condition that is normally treated with a prescription medication that could lead to physical or psychological dependence, when a physician determines that medical use of marijuana would serve as a safer alternative to the prescription medication
- ▶ A terminal illness
- ▶ Any other chronic, debilitating or other medical condition, including, but not limited to, hepatitis C, ALS, inflammatory bowel disease, Crohn's disease, Huntington's disease, autism, neuropathies, sickle cell anemia, agitation of Alzheimer's disease, cachexia, and wasting syndrome.

# Missouri Patients in 2021

## Condition

- ▶ Physical/Psychological Dependence - 30%
- ▶ Chronic Medical Condition - 28%
- ▶ Psychiatric Disorders - 17%
- ▶ Migraine HA - 6%
- ▶ Terminal Illness - 3%
- ▶ Other Conditions - 16%

## Age

Under 17 - 0.31%

18-29 - 15%

30-39 - 25%

40-49 - 20%

50-59 - 18%

60-69 - 17%

70 and up - 5%

# Top 10 Conditions to Know

- ▶ Pain/Chronic Pain
- ▶ Insomnia
- ▶ Depression
- ▶ Anxiety
- ▶ Muscle Spasm
- ▶ Headache/Migraine
- ▶ Nausea
- ▶ Cancer
- ▶ Anorexia
- ▶ PTSD



# Pain

72% to 90% of medical cannabis patients listed pain as a qualifying condition.<sup>1,2</sup>



# Pain

- ▶ The effect of cannabis and cannabinoids on pain have been well documented.<sup>3-8</sup>
- ▶ Pain isn't pain until it reaches the brain. Prior to that it is nociception.
- ▶ THC and CBD have different effects on pain.
- ▶ Both THC and CBD inhibit glutamate neurotoxicity, are neuroprotective, and are antioxidant, all of which improve neuropathy, and may reduce neuropathic pain.
- ▶ THC is a known CB agonist. Similar effect as endocannabinoid CB agonism, to promote antinociception and inhibit neuronal excitability.
- ▶ CBD might inhibit hyperanalgesia acting through non-CB receptors such as TRPV1, or alpha glycine receptors, or it might support EC function by inhibiting degradation.
- ▶ THC is effective at treating neuropathic and inflammatory pain.
- ▶ CBD is effective at treating inflammatory pain.

# Chronic Pain

- ▶ Chronic pain is a condition where patients are often focused on primarily managing their pain above and beyond the underlying causative condition(s). In this case they seek help for the condition of “pain management” which is multifactorial.
- ▶ Chronic pain is complex and can result from nociceptive, inflammatory, peripheral and/or centralized pain mechanisms. Cannabis manages chronic pain in part, by preventing peripheral nociception from reaching the brain.
- ▶ In addition to changes in pain perception, there is also the possibility of change in attitude.

# Chronic Pain

- ▶ The much hoped for efficacy of THC for pain management seems to be limited to chronic, not acute pain, although there are conflicting reports, and dosage is critical.<sup>9,10</sup>
- ▶ The overly attributed efficacy of CBD for pain management has not clearly been confirmed when in pure form. Using purified CBD, it was reported that, “CBD showed no analgesic action of its own in a clinical study using a daily dose of 450 mg CBD.”<sup>4</sup>
- ▶ Cannabis extracts are more effective than pure isolates and can provide mixed cannabinoids.
- ▶ The effectiveness of full extract cannabis is a product of synergy between the cannabinoids and the terpenes.
- ▶ Beta-caryophyllene is an anti-inflammatory terpene.

# Insomnia

71% of medical cannabis patients listed insomnia as a qualifying condition, 14% as the main symptom for which they were seeking care.<sup>1</sup>



# Insomnia

- ▶ The EC system regulates the circadian sleep-wake cycle. Chronic use of cannabis, which downregulates EC activity, may disrupt sleep in the long term.<sup>11</sup>
- ▶ The type of cannabinoids (THC, CBD), ratio of cannabinoids, dosage, timing of administration, and route of administration all determine efficacy.<sup>12</sup>
- ▶ THC causes a mild decrease in REM sleep in low doses, increases deep sleep or total sleep time at first, and decrease both REM and deep sleep at high doses.
- ▶ A corollary effect of decrease in dreams, including nightmares, has been a benefit for patients with PTSD.
- ▶ These effects may diminish with tolerance.
- ▶ CBD has sedative and anxiolytic properties depending on the dose. Lower doses may contribute to wakefulness, higher doses may cause somnolence or no effect.<sup>13</sup>

# THC/CBD for Sleep

8 healthy volunteers were given 4 treatments - placebo or

- ▶ 15 mg THC
- ▶ 5 mg THC plus 5 mg CBD
- ▶ 15 mg THC plus 15 mg CBD

15 mg THC did not increase sleep time but did increase the duration of deep slow wave sleep.

- ▶ The next day -

With 15 mg THC, memory was impaired, sleep latency was reduced, and subjects reported increased sleepiness and changes in mood.

With 5 mg THC and 5 mg CBD or 15 mg THC and 15 mg CBD, there was a decrease in stage 3 sleep.

With the higher dose combination, wakefulness was increased.

- ▶ 15 mg THC appears to be sedating
- ▶ 15 mg CBD appears to have alerting properties.<sup>14</sup>

# Insomnia

- ▶ 1:1 CBD/THC - “Sativex, while having little effect on the recorded sleep hours, rather produced marked changes in reported sleep quality.”<sup>15</sup>
- ▶ It’s important to use cannabis in a long-acting form, such as capsules, edibles or tincture if you find you’re waking up in the middle of the night.
- ▶ “Indica” strains have been thought to be more sedating - actually, myrcene and humulene are the sedating terpenes.
- ▶ Preparations containing the CBN, even in small amounts may be effective.
- ▶ A patient’s tolerance to cannabis, the dose of THC, the dose of CBD, and the presence of sedating terpenes such as myrcene, all contribute to the efficacy of cannabis as a sleep-inducing agent.



# Depression

Up to 50% of medical cannabis patients list depression as a qualifying condition.2



# Depression

- ▶ The debate about whether cannabis helps depression or might cause it has been going on for as long as cannabis has been considered a drug of abuse.
- ▶ Studies have tried to show that cannabis can harm your mood, especially in youth. But this has not been borne out with adjustment for other risks.
- ▶ Clinical depression is hypothesized to be linked to EC dysregulation. Depressed patients have reduced levels of ECs.<sup>16</sup>
- ▶ In an animal study using cannabinoid agonists, low doses elicited antidepressant-like behavior and enhanced 5-HT neurotransmission, while high doses attenuated 5-HT neurotransmission. They concluded “It is becoming apparent that the correct dosage is important in mood control.”<sup>17</sup>
- ▶ “High doses 1.25, 2.5, and 5 mg/kg of  $\Delta^9$ -THC showed a U-shaped dose response, with significant antidepressant-like effects at 2.5 mg/kg”.<sup>18</sup>

# Depression

- ▶ Patients treated with 2.5 mg to 7.5 mg of dronabinol per day, almost 80% patients showed improvement of depressed mood.<sup>19</sup>
- ▶ In mice, high doses of CBD (50mg/kg) were found to exert antidepressant-like effects. CBD significantly enhanced serotonin and glutamate levels which were prevented by 5-HT1A receptor blockade.<sup>20</sup>
- ▶ The terpene profile is also most important in mood effects. Strain selection is important, because strains that are too sedating may contribute to the lethargy of depression and could accentuate dysfunctional symptoms. In general sativa dominant strains are more uplifting.
- ▶ Limonene elevates mood and assists in the absorption of other terpenoids.
- ▶ Pinene can boost energy and is said to improve concentration.
- ▶ The conflicting results of cannabis effect on depression depends on several variables. The internal endocannabinoid tone of the patient, the dose, chronicity and type of cannabis used, and the type of depression.

# Anxiety

Up to 58% of medical cannabis patients list anxiety as a qualifying condition.<sup>2</sup>



# Anxiety - THC

- ▶ Studies on the psychological effects of cannabis and its effect on anxiety have been many, contradictory, and more often done with THC-rich cannabis.
- ▶ A recent survey, medical cannabis users perceived a 58% reduction in anxiety. Two puffs were sufficient. CBD (> 11%)/high THC (> 26.5%) cannabis produced the largest perceived changes in stress.<sup>21</sup>
- ▶ Effects of THC on the EC system - it is a CB agonist, and its stimulation of CB receptors shows a bidirectional dose response. Low doses of CB1 receptor agonists elicit anxiolytic effects, while high doses are anxiogenic.<sup>22,23</sup>
- ▶ The therapeutic range for THC to be anxiolytic might be less than 10-15 mg. This is not directly translatable to cannabis with the added effect of terpenes making some cultivars more effective at lower doses than others.
- ▶ Mechanisms of the effects of cannabinoids on anxiety-related responses involve CB1 and non-CB1 receptors, including the 5HT1A receptor.<sup>24</sup>

# Anxiety - CBD

- ▶ Since the anxiolytic effects of CBD became known, interest in the therapeutic use of cannabis for anxiety has grown.
- ▶ CBD, an allosteric modulator at CB receptors, also has activity at the 5HT-receptors among others.<sup>25</sup>
- ▶ CBD (300 mg) was as effective as the two known anti-anxiety medicines.<sup>26</sup>
- ▶ CBD actions also have a dose dependent response. Anxiety was reduced with CBD 300 mg, but not with CBD 100 and 900 mg.<sup>27</sup>
- ▶ This is not directly translatable to cannabis with the added effect of terpenes making some cultivars more effective at lower doses than others.
- ▶ CBD can counteract the anxiogenic effect of THC. The increased anxiety following the administration of THC (0.5 mg/kg) was significantly attenuated with the simultaneous administration of CBD (1 mg/kg).<sup>28</sup>
- ▶ The terpene profile is most important in mood effects. Linalool is the terpene most associated with effectiveness for anxiety.

# Muscle Spasm

10% to 18% of medical cannabis patients listed muscle spasm/spasticity as a qualifying condition.<sup>1,2</sup>



# Muscle Spasm/Spasticity

- ▶ Muscle spasm is a common component of many types of acute and chronic pain.
- ▶ The EC system affects muscle contractility. In visceral smooth muscle, stimulation of CB1 and CB2 receptors with ANA resulted in marked relaxation of contraction.<sup>29</sup>
- ▶ Although there are many anecdotal reports of relief from muscle spasms using cannabis, modern research is surprisingly sparse.
- ▶ In one case report muscle spasm in the legs secondary to a chemotherapy drug, was 100% resolved with cannabis. The patient used 1 joint 3-4 times/day. Baclofen and cyclobenzaprine were not successful.<sup>30</sup>
- ▶ THC was found to be significantly better than codeine in reducing muscle spasm in a paraplegic patient.<sup>31</sup>

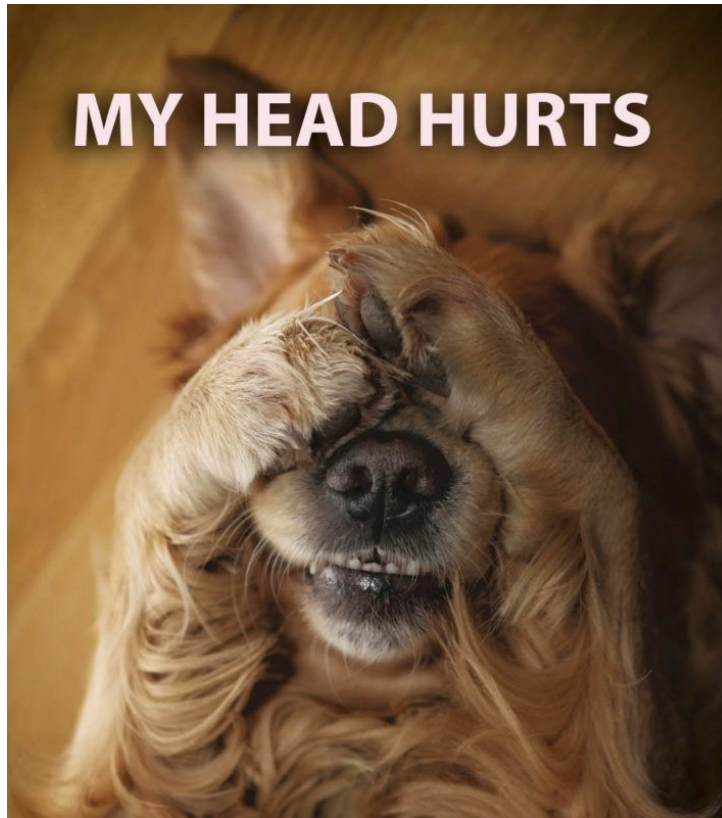


# Muscle Spasm/Spasticity

- ▶ Spasticity is found in several neurologic disorders that cannabis treats, especially multiple sclerosis (MS). Most studies done with cannabis extracts.<sup>32</sup>
- ▶ In the MUSEC 12-week trial, the rate of relief from muscle stiffness was almost twice as high with cannabis extract vs. placebo, 30% relief vs. 16%.<sup>33</sup>
- ▶ In a study of smoked cannabis by MS patients the Ashworth scores decreased almost 3 points in a 10-point scale.<sup>34</sup>
- ▶ Central and peripheral cannabinoid receptors are involved in anti-inflammatory and analgesic effects.<sup>34</sup> Not only cannabinoid agonists such as THC, but CBD is effective topically as well.
- ▶ Often topical application of cannabis is used for muscle relaxation, applied to the affected area without causing psychoactive effects. Widespread spasticity requires internal use.

# Headache/Migraine

15% to 35% of medical cannabis patients listed headache or migraine as a qualifying condition.<sup>1,2</sup>



# Headache

- ▶ Cannabis has long been known as a botanical medicine that could relieve headache.<sup>36</sup>
- ▶ Headaches usually involve overactivation of the trigeminovascular pathway, an area of the brain under EC regulation.<sup>37,38</sup>
- ▶ One theory of headache pathogenesis is the Clinical Endocannabinoid Deficiency Syndrome.<sup>39</sup> Lowered EC levels are found in headache patients.<sup>40</sup>
- ▶ There have been few studies using cannabinoids or cannabis to treat headaches.
- ▶ Nabilone (0.5 mg/day) was slightly better than ibuprofen for migraine and medication overuse HA.<sup>41</sup>
- ▶ Another study showed effectiveness of a THC/CBD mix at high doses.<sup>42</sup>

# Headache

- ▶ 90% of patients with migraine used cannabis for treatment and prophylaxis with frequency decreasing from 10.4 to 4.6 headaches/month.<sup>43</sup>
- ▶ Patients report that if cannabis is taken at the onset of the headache, the headache will not occur, or that the severity or frequency is lessened. Also, they have less stress and better sleep with cannabis use.
- ▶ It is important to use cannabis at the earliest signs of the start of a migraine, to arrest the progression into a full-blown headache. Tinctures are available absorbed under the tongue (sublingual) and work in minutes. Inhalation through a vaporizer or smoking can produce even more rapid relief.
- ▶ Cannabis can also treat muscle cramps (particularly of the neck and shoulders), and as in tension headaches. It can be used internally and topically, applied directly to the site of tension.

# Nausea

3% to 27% of medical cannabis patients listed nausea as a qualifying condition.<sup>1,2</sup>



*"Nausea is the other side effect."*

# Nausea

- ▶ Cannabis has been used since ancient times to treat nausea.
- ▶ The EC system and cannabinoids are involved in regulating nausea and vomiting. The action of cannabinoids on CB receptors in the brainstem and/or on vagal pathways is proposed as one mechanism of action.
- ▶ THC is approved in the US since 1985 as dronabinol for treatment of chemotherapy-associated nausea and vomiting (CINV).
- ▶ CBD is thought to reduce nausea by interacting with serotonin receptors through another mechanism. CBD was shown to suppress nausea and vomiting within a limited dose range (in animal model).<sup>44</sup>
- ▶ The effect of CBD on toxin-induced vomiting displays a biphasic response with low doses producing an anti-emetic effect and higher doses enhance vomiting.
- ▶ Animal studies suggest that CBDA is also effective to treat nausea.<sup>45</sup>

# Nausea

- ▶ In a study of CINV, absence of nausea was 71% with dronabinol, 64% with ondansetron, 15% with placebo.<sup>46</sup>
- ▶ A nabiximol, (CBD/THC 1:1) has been found to decrease CINV in preclinical trials.<sup>47</sup>
- ▶ Cannabis has been documented as effective treating nausea in HIV patients.<sup>48</sup>
- ▶ Chronic use of cannabis is at risk for developing tolerance, potentially causing dysfunction in an autonomic response such as N/V - i.e., patients can develop nausea on withdrawal of cannabis.
- ▶ Good methods of delivery include inhalation or sublingual products, to avoid loss of ingested medicine due to vomiting. Rectal administration would also work, but these cannabis products are limited in availability.

# Cannabinoid Hyperemesis Syndrome

- ▶ **A paradoxical effect of cannabinoids** on vomiting has been proposed as a possible explanation for the cannabinoid hyperemesis syndrome (CHS).
- ▶ This occurs episodically or cyclically, and usually in people who have a higher chronic use of cannabis. Ninety-five percent of CHS patients were found to cannabis daily, for 10 years before symptom onset.
- ▶ The pathogenesis of paradoxical hyperemetic symptoms of CHS remain unclear.
- ▶ Abstinence from THC-rich cannabis resolves the condition. This definitely qualifies as an adverse effect of using cannabis.<sup>49-51</sup>



# Cancer

1% to 10% of medical cannabis patients listed cancer as a qualifying condition.<sup>1,2</sup>



# Cancer

## Treating the Symptoms of Cancer and Cancer Therapies

- ▶ Cannabis is approved most often to treat the symptoms of cancer or its therapies, such as pain nausea, vomiting, loss of appetite, low mood, poor sleep, and neuropathy.
- ▶ “For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression. Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy.”<sup>52</sup>

# Cancer

## Treating Cancer

- ▶ Cannabinoid receptors are upregulated in tumor tissue. the EC system may be over-activated in cancer and may be pro-tumorigenic.<sup>53</sup>
- ▶ Conversely, the activation of cannabinoid receptors reduces tumor growth. The upregulation of EC degrading enzymes has been observed in aggressive human tumors and cancer cell lines.<sup>53</sup>
- ▶ Cannabinoids, including THC and CBD have anti-tumoral properties, which is often cell type specific.
- ▶ To achieve clinical success very high doses of cannabis/cannabinoids are required. This involves a process that is experimental, complicated, costly, and variable clinically. Patients should not do this without professional advice.

# Anorexia

2% to 10% of medical cannabis patients listed anorexia as a qualifying condition.<sup>1,2</sup>



# Anorexia

- ▶ Cannabis for appetite stimulation in the case of cachexia, malnutrition and weight loss associated with cancer, chemotherapy, or HIV/AIDS is well known.
- ▶ Patients use cannabis to stimulate appetite in more widespread problems, such as disinterest in food, the effect of stimulants, stress, or as a side effect of some medications, or in the extreme case of anorexia nervosa.
- ▶ The EC system is intricately involved in the regulation of the “hunger hormones,” ghrelin and leptin.<sup>54</sup>
- ▶ Activation of cannabinoids drives the release of leptin and ghrelin. THC is thought to exert these effects by binding to CB1 receptors.
- ▶ The stimulating effect of THC is more pronounced at lower as compared to higher doses, implying a biphasic dose response. In mice, lower doses of THC increased feeding while higher doses decreased feeding.<sup>54</sup>
- ▶ CBD does not acutely stimulate appetite and may antagonize weight gain, but is anxiolytic for Anorexia Nervosa patients.

# Anorexia

- ▶ The effects of dronabinol 2.5mg 2x/day, or cannabis, in HIV patients showed modest or no effect on weight gain, vs. placebo weight loss.<sup>55,56</sup>
- ▶ In cancer patients enhanced chemosensory perception of food with dronabinol 2.5 mg 2-3x/day. Appetite and caloric intake increased, but no weight gain.<sup>57</sup>
- ▶ Smoked cannabis, several cigarettes per day promoted increased eating and a body-weight increase, 2-3 kg in 3 weeks.<sup>58</sup> Not all studies show weight gain.
- ▶ Anorexia nervosa patients treated with THC showed improvement in depression and perfectionism, with a minimal weight gain, 0.95 kg over 4 weeks.<sup>59</sup>
- ▶ Tolerance is a factor. **One adverse effect of chronic cannabis use is the development of lack of appetite unless it is stimulated by cannabinoids.**
- ▶ There is also variation in strain specificity. Cultivars high in humulene may actually suppress appetite.

# PTSD

25% to 33% of medical cannabis patients listed PTSD as a qualifying condition in states where it is approved.



# PTSD

- ▶ Cannabinoid agonists including THC, can impair memory retrieval while facilitating memory extinction, attenuate the excessive retrieval of trauma experienced in PTSD.<sup>60</sup>
- ▶ CBD may also play a role in trauma relief. CBD, 32 mg by inhalation, was found to facilitate the extinction of aversive conditioning, but only when administered immediately after, and not before the process.<sup>61</sup>
- ▶ THC or its analogs might help sleep in PTSD patients. Nabilone, a cannabinoid agonist, decreased treatment resistant nightmares in PTSD subjects.<sup>62</sup>
- ▶ Patients taking 5 mg THC sublingual 2x/day, showed improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms.<sup>63</sup>
- ▶ THCV may combat anxiety and panic attacks, while stimulating CB receptors (to address stress), with potential use for those who suffer from PTSD.



# PTSD

- ▶ “Current literature is suggestive of a potential decrease in PTSD symptomatology with medical marijuana, but also suggests a correlation with problematic cannabis use.”<sup>64</sup>
- ▶ Confounding from many studies have correlated an increase in cannabis use disorder, especially in veterans with PTSD. Many of these patients have been classified as substance abusers rather than medical patients.
- ▶ The VA has issued a new policy, as of December 2017. It states "Veterans must not be denied VHA services solely because they are participating in State-approved marijuana programs." It also encourages veterans to discuss medical marijuana use with their VA providers.
- ▶ An important corollary is that their cannabis use should ordinarily no longer automatically be considered as a disorder.

# Summary

- ▶ Become trained in the effects and dosing of cannabis for the qualifying conditions in your patient population.
- ▶ Pain is the most common condition for which patients use cannabis. THC is analgesic; CBD and THC are anti-inflammatory,
- ▶ Insomnia is a common use of cannabis; consider THC-rich with myrcene.
- ▶ Depression and anxiety are often co-diagnosed. Choose cultivars carefully: CBD is generally used for anxiety, THC for depression.
- ▶ Muscle spasm responds to THC and CBD; spasticity requires internal use.
- ▶ HA, use of THC at start of migraine; topical for tension HA.
- ▶ N/V, many cannabinoids effective, THC, CBD, CBDA; use sublingual or rectal.
- ▶ Cancer, cannabis most often used to treat symptoms.
- ▶ Anorexia, THC stimulates appetite; CBD is anxiolytic for Anorexia Nervosa.
- ▶ PTSD, THC and THCV regulate the stress response; THC helps reduce nightmares.

# Thank You

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**You can't spell  
healthcare without  
"THC."**