White Paper on Medical Cannabis

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Over the past 50 years, neuroscience and biochemistry has advanced our understanding of the body's inherent endocannabinoid system and the importance that this widespread receptor system plays in the homeostasis of a broad variety of biological systems. The CB1 and CB2 receptor systems were discovered in the early 1990s, and their activating ligands, anandamide and 2-Arachidonoylglycerol, were isolated shortly thereafter, prompting more in-depth research and analysis.

Delta-9 THC (Δ-9-THC) and its entourage of cannabinoids and terpenoids have been shown to affect multiple homeostatic mechanisms such as sleep, muscle tone, mood, appetite, pain modulation, and inflammation. However, it is important to understand that these effects are not always beneficial. As with any homeostatic mechanism, an appropriate balance is paramount. Too much or too little stimulation can create an imbalance and subsequent dysfunction in this delicate system.

Chronic and excessive use may create tolerance of this dynamic receptor class. As CB1 and CB2 receptors become saturated and overstimulated by the phytocannabinoids contained within cannabis, tolerance to the body's own endocannabinoid system will develop, thus creating a rebound effect. Much like opioids and benzodiazepines, cannabis, with chronic overuse, may worsen the exact symptoms that are intended to be treated. Any stimulus that affects the pain/pleasure balance of consciousness (i.e., hedonic tone) will elicit compensatory adaptation by the central nervous system that is precisely the opposite effect of the stimulus.

Based upon the largest and most recent national surveys, between 9.3% and 30.6% of Americans who use cannabis at least once will develop cannabis use disorder (CUD) sometime in their life. The risk of CUD varies greatly based upon a variety of factors which include age of first use, frequency and amount of use, and the THC/CBD ratio of the chemovar. The route of administration may also influence the risk of development of a cannabis use disorder. The more rapid the onset of reward following the administration of the molecule, the more reinforcing the behavior will become. This process, known as operant conditioning, suggests that intravenous and pulmonary routes of administration tend to be more rapid and addictive than slower routes, such as oral or topical administration.

Younger brains tend to adapt to compulsive use of cannabis more readily than more mature and developed brains because the prefrontal cortex has not completely developed until after the age of 25. For this reason, it is recommended that chronic use of medical cannabis be reserved only for palliative care or end-of-life scenarios in patients under the age of 25.

The human brain exhibits a relatively low CB1 receptor density in the brain stem, suggesting that life-threatening CNS depression with cannabis is not a significant clinical risk. The toxic effects of Delta-9 THC may, however, result in significant psychosis and a subsequent risk of injury or accident. The Delta-8 and Delta-10 molecules may also result in similar symptoms with toxicity. Cannabidiol, benzodiazepines, or antipsychotic medications may be used to treat the symptoms of acute THC-induced psychosis in emergent situations when simple reassurance fails.

Synthetic cannabinoid such as “spice” and K2 are known for their potent psychoactive effects which may elicit psychosis at certain levels. THC toxicity may be dependent upon the potency of the THC/CBD ratio or simply the dose concentration of the product itself. Edibles, particularly in the novice user, may result in THC toxicity more commonly than other faster delivery systems. This slower onset of action created by oral administration may also lead to toxicity. Patients will often use excessive amounts of edible cannabis products believing that the product is having no or little effect initially.

Due to the synergistic effects on the reward circuits of the brain, concomitant use of other controlled substances with medical cannabis is ill-advised. DEA-scheduled medications such as opioids, benzodiazepines, Z-drugs, and amphetamine salts all increase the levels of dopamine in the neuronal synapses of the nucleus accumbens and elicits changes in the caudate nucleus and other cortico-basal structures, including the prefrontal cortex of the brain. Combinations of substances that activate the dopaminergic reward center, such as benzodiazepines, opioids and amphetamine derivatives should be avoided in combination with chronic medical cannabis, except in end-of-life scenarios. In such palliative care cases, comfort may often be prioritized over long-term functionality.

Unwanted side effects may be mitigated or therapeutic benefits may be enhanced by controlling the chemical content of cannabis. The THC to CBD ratio may be altered to increase or decrease the psychological effects of medical cannabis. Some chemovars may provide sedation while others provide mental focus and enhanced cognition. Some may provide muscle relaxation while others offer more anti-inflammatory effects. For this reason, certifying physicians should be familiar with the principles of the entourage effect of cannabis and its components before certifying patients for use. Certifying providers for medical cannabis should be able to advise

their patients on proper chemovar selection to enhance the benefit of the intended therapy and to mitigate the risks of unwanted side effects.

As a matter of practice congruent to any other pharmacologic treatment, providers should only certify medical cannabis treatment after an appropriate discussion including informed consent with the patient about the potential risk/benefit ratio of therapy before entering into a formal, signed treatment agreement. The treatment agreement should include the following:

1.) Specify the prohibition of the combined use of other controlled substances such as opioids, benzodiazepines, Z-drugs, barbiturates, and amphetamine derivatives, except for emergency use. (In emergent cases, all providers of controlled substances should be made aware of this combination, and the combination should be discontinued as soon as feasible.)
2.) Close monitoring of such combinations is indicated, and the combination should be used for the shortest duration possible.
3.) The relationship between the certifying provider and the patient is that of an equal partnership requiring unanimous agreement to initiate or continue any treatment.
4.) If either party feels that the risk/benefit ratio is no longer favorable, each has the right and the duty to discontinue therapy.

As in the case of other controlled substances, tolerance and tachyphylaxis with medical cannabis is common with chronic use. To combat the diminishing effectiveness of cannabis therapy in chronic use, experienced providers may adapt a combination strategy with other controlled substances on a rotational schedule. With this approach, careful monitoring should seek to reduce the risk for simultaneous use of dopaminergic-enhancing drugs in combination. The exception to this rule would be in palliative care or end-of-life scenarios.

Other recommendations would be as follows:

1.) Certifying providers should treat medical cannabis as a Schedule II DEA controlled medication.
2.) Certifications should not extend beyond a monthly recall.
3.) The PDMP should be checked with each visit, and a random drug screen should be obtained at least 6 times per year.
4.) Patients should be required to bring the chemical content analysis of the cannabis product last purchased to each visit.

5.) Proof of purchase, including the quantity of product dispensed and its delivery method should be required for each visit. This information should be entered into the patient's medical record.
6.) PDMP historical activity that includes controlled substances should prompt a discussion with the patient regarding the terms of the signed treatment agreement and consideration for referral to a qualified addiction specialist.
7.) Continued monthly recertification for medical cannabis should be contingent upon the patient's compliance with the treatment agreement over the risk/benefit ratio of the content analysis and amount of product being consumed by the patient as well as any intended or unintended effect from the product.

It is not the responsibility of the certifying provider to enforce federal, state, or local law. It is, however, the duty of the provider to first do no harm *("primum non nocere")*. As medical managers of a DEA-controlled substance, clinicians must strive to protect the patient and public health alike. The treatment agreement and clinical policy of the certifying provider should show an intent to protect the public from diversion and the patient from abuse of the substance to which the patient is being exposed. Surveillance should involve PDMP monitoring, drug testing, and frequent physical and mental assessment. Documentation should include at minimum, a physical examination, mood and mental status, and social interaction/behavior with others.

While the risk of overdose death of cannabis alone is very low, harm remains a legitimate concern and must be considered. The certifying provider and the patient have a joint duty to discontinue treatment if the risk/benefit ratio is determined to no longer be favorable. If assistance with cannabis cessation is necessary, the certifying provider should either provide such assistance or refer patient to a qualified addiction specialist.

Chronic cannabis use may result in a rebound neuronal adaptation effect potentially causing consequences including, but not limited to insomnia, depression, anxiety, and suicidal ideation. Careful monitoring and response to the dynamic components of the realm of the biopsychosocial disease management is the best practice approach. In addition, it is a consensus recommendation that medical cannabis be avoided entirely in the pregnant patient or in those actively trying to conceive.