

## Flexible Replacement and Expedited Discontinuation of Opioid Medication (FREEDOM) Protocol

### INTRODUCTION

The field of Cannabis-Based Medicine (CBM) is a rapidly developing one, and a field that attracts the attention of both the medically conservative and progressive.<sup>1,2</sup> The most frequently claimed indication for the use of medical cannabis in applicable states is pain relief, and the scientific evidence supporting this indication is substantial and growing.

Nationwide, medical groups and patient advocacy groups alike have voiced concerns regarding what could be considered a public health epidemic of opioid misuse and consequent fatal overdoses.<sup>3,4</sup> Posted figures are staggering—over 14,000 Americans died from prescription opioid overdose<sup>5</sup> in 2014 alone, and rates are on the rise. The CDC recently released guidelines regarding restricted use of opioids for pain control<sup>6</sup> recommending non-opioid treatments as first-line therapy;<sup>7</sup> however, implementation of these guidelines will impact millions of patients currently maintained on chronic opioids and specific guidelines for opioid discontinuation are lacking. Meanwhile, a thousand patients are treated in US emergency departments every day for opioid misuse.<sup>8</sup>

Taken together, it is clear that millions of Americans suffer from pain, yet further suffer from inadequate conventional pain treatment with opioids. In light of potential evidence supporting cannabis as a sustainable option for pain management, the lack of fatal cannabis overdoses, and the observation that opioid overdose fatalities decrease in states where medical cannabis is available,<sup>9</sup> we, the physicians at Vireo Health, developed the FREEDOM protocol. While there are no black-and-white answers to this multifactorial morass, we believe that spearheading an effort to incorporate the adjunctive use of cannabis in states in which it is

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<sup>1</sup> Marijuana and Medicine Assessing the Science Base Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., Institute of Medicine, 1999

<sup>2</sup> Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA*. 2015;313(24):2474-2483. doi:10.1001/jama.2015.6199

<sup>3</sup> <http://www.hhs.gov/opioids/about-the-epidemic/>

<sup>4</sup> Volkov ND, Frieden TR, Hyde PS and SS Cha (2014). Medication-Assisted Therapies – Tackling the Opioid-Overdose Epidemic. *The New England Journal of Medicine* 370(22): 2063- 2066

<sup>5</sup> <http://www.cdc.gov/drugoverdose/data/overdose.html>

<sup>6</sup> <http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1er.htm>

<sup>7</sup> Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *JAMA*. Published online March 15, 2016. doi:10.1001/jama.2016.1464

<sup>8</sup> Substance Abuse and Mental Health Services Administration. Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. The DAWN Report. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2013. Available from URL: <http://www.samhsa.gov/data/2k13/DAWN127/sr127-DAWN-highlights.htm>

<sup>9</sup> Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern Med*.2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005

legal, to both reduce opioid use and promote pain management, is of immediate need, and will demonstrate long-term value.

## BACKGROUND

While human trials are limited,<sup>10</sup> animal studies show that cannabinoids and opioids simultaneously trigger analgesia through a G-protein-coupled mechanism blocking the release of pain-propagating neurotransmitters in both the brain and spinal cord.<sup>11</sup> The clinical validation of CBM therapy in the treatment of pain and the subsequent potential to decrease opioid use is rapidly progressing.<sup>12,13</sup> It is well-documented that THC enhances the potency of opioids such as morphine in animal models, supporting an intimate connection between cannabinoid and opioid signaling pathways in the modulation of pain perception.<sup>14,15,16</sup>

Chronic pain treatment can be a comprehensive undertaking for medical providers and patients alike, extending beyond medication management alone.<sup>17</sup> Currently over 10% of the US population suffers from non-acute pain,<sup>18</sup> and 3-4% are maintained on chronic opioids despite unproven benefits for opioids in chronic pain.<sup>6,19</sup> Unfortunately, in addition to the risk of overdose, routine opioid treatment is also associated with side effects such as pruritis, sedation, nausea and constipation.<sup>20,21,22</sup>

The aim of the FREDOM protocol is to support novel potential analgesic regimens in eligible patients by potentially incorporating CBM. We aim for this protocol to support clinical

<sup>10</sup> Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011 Nov;72(5):735-44. doi: 10.1111/j.1365-2125.2011.03970.x

<sup>11</sup> M. Shapira, M. Gafni, Y. Sarne. Long-term interactions between opioid and cannabinoid agonists at the cellular level: cross-desensitization and downregulation. *Brain Research*, 960 (2000), pp. 190–200

<sup>12</sup> Haroutounian S, et al. The Effect of Medicinal Cannabis on Pain and Quality of Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain*. 2016 Feb 17. [Epub ahead of print]

<sup>13</sup> Meng, H., Hanlon, J. G., Katznelson, R., Ghanekar, A., McGilvray, I., & Clarke, H. (2016). The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: A case report. *Canadian Journal of Anesthesia*, 63(3), 307-310. doi:10.1007/s12630-015-0525-6

<sup>14</sup> D.L. Cichewicz, Z.L. Martin, F.L. Smith, S.P. Welch. Enhancement of  $\mu$  opioid antinociception by oral  $\Delta$ 9-tetrahydrocannabinol: dose–response analysis and receptor identification. *Journal of Pharmacology and Experimental Therapeutics*, 289 (1999), pp. 859–867

<sup>15</sup> R. Mechoulam, N. Lander, M. Srebnik, I. Zamir, A. Breuer, B. Shalita, S. Dikstein, E.A. Carlini, J.R. Leite, H. Edery, G. Porath. Recent advances in the use of cannabinoids as therapeutic agents. S. Agurell, W. Dewey, R. Willette (Eds.), *The Cannabinoids: Chemical, Pharmacological and Therapeutic Aspects*, Academic Press, New York (1984), pp. 777–793

<sup>16</sup> Abrams, D. I., et al. "Cannabinoid–opioid interaction in chronic pain." *Clinical Pharmacology & Therapeutics* 90.6 (2011): 844-851.

<sup>17</sup> Scascighini, L., Toma, V., Dober-Spielmann, S., & Sprott, H. (2008). Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology*, 47(5), 670-678.

<sup>18</sup> Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*. 2015;16(8):769-780

<sup>19</sup> Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf*. 2009;18(12):1166-1175

<sup>20</sup> Furlan, Andrea D., et al. "Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects." *Canadian Medical Association Journal* 174.11 (2006): 1589-1594.

<sup>21</sup> McNicol, E., Horowicz-Mehler, N., Fisk, R. A., Bennett, K., Gialeli-Goudas, M., Chew, P. W., ... & Carr, D. (2003). Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *The Journal of Pain*, 4(5), 231-256.

<sup>22</sup> Ricardo Buenaventura, M., Rajive Adlaka, M., & Nalini Sehgal, M. (2008). Opioid complications and side effects. *Pain physician*, 11, S105-S120.

efforts to utilize CBM as a possible adjunctive therapy to decrease harm associated with opioids, especially pain that may be resistant to opioids treatment alone, patients at higher risk of death from opioid use, and patients in whom opioid use markedly diminishes quality of life.

There are two major goals for the FREEDOM protocol, with three supportive measures:

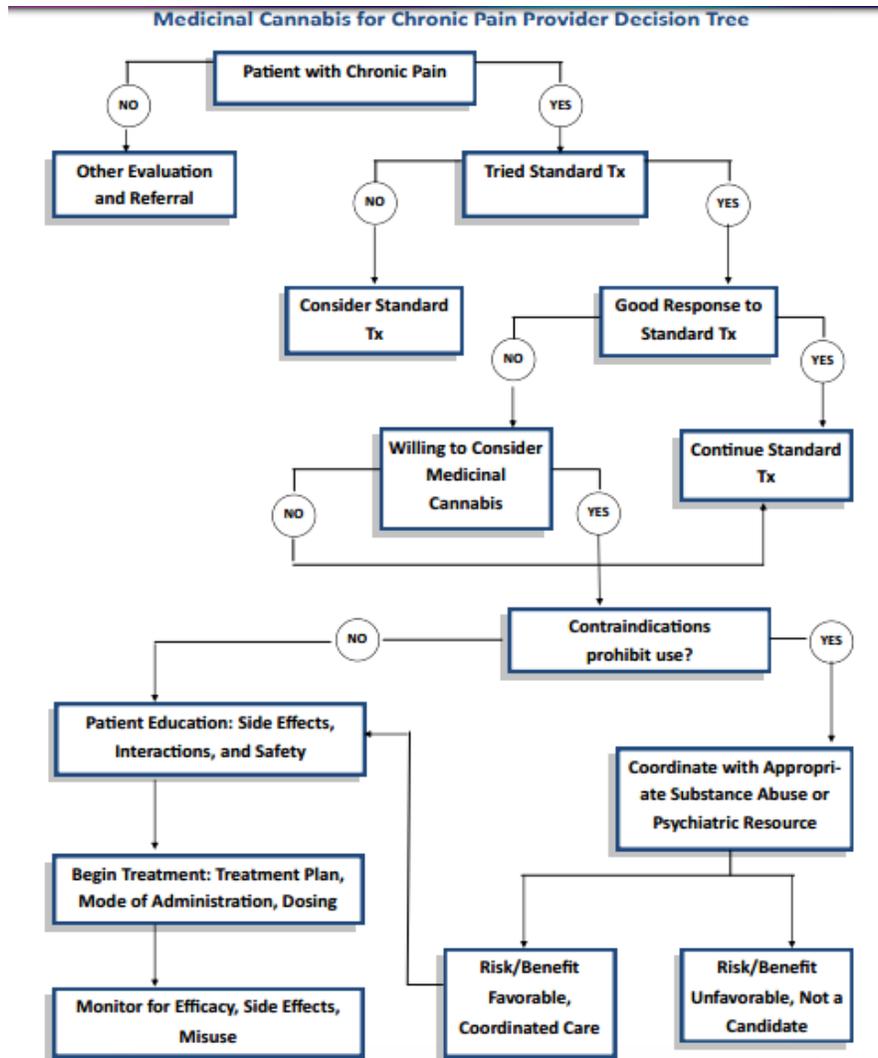
1. Control and/or reduction of pain
2. Opioid reduction or cessation
  - Monitoring and minimization of opioid withdrawal symptoms
  - Monitoring and minimization of opioid side effects and other negative effects
  - Monitoring and minimization of CBM side effects

Consistent with our overall strategy in CBM to “start low and go slow,” we encourage this transition to be intimately overseen by the patient’s care team and implemented slowly over an appropriate period of time. To date, there is no proven standard opioid tapering protocol in widespread use, and none that offer cannabis as supportive therapy for potential pain control during the opioid tapering period. Individual decisions to speed up or slow down the protocol will be made by the physician in conjunction with patient feedback. We offer a flexible potential strategy, based on our own increasing experience with CBM to support both physicians and their patients and offer more diverse, yet safe treatment options in pain management. The FREEDOM protocol is not a proven detoxification plan and acts only as broad guide for physicians looking to utilize CBM while simultaneously considering a reduction in opioid dosage for patient safety.

## CBM INITIATION, PATIENT TITRATED DOSING, AND INITIAL OPIOID REDUCTION

To initiate CBM, a patient must not only have a qualifying condition as determined by their physician in their state of residence,<sup>23,24</sup> but must also be deemed a good candidate for CBM use by their primary physician as depicted in Figure 1.

Figure 1



Adapted from Grant I, Atkinson JH, Gouaux S, Wilsey B. Medical marijuana: clearing away the smoke. *Open Neurol J* 2012;6:18-25. Free online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358713/pdf/ONJ11-6-18.pdf>

<sup>23</sup> <http://www.health.state.mn.us/topics/cannabis/rulemaking/index.html>

<sup>24</sup> [https://www.health.ny.gov/regulations/medical\\_marijuana/regulations.htm](https://www.health.ny.gov/regulations/medical_marijuana/regulations.htm)

Once it is determined that a patient is a good candidate and willing to explore the therapeutic use of medical cannabis as a potential adjunct for pain treatment, the patient must be fully educated on risks and benefits as would be undertaken with any new medical treatment regimen.

In order to be successful in a protocol such as FREDOM, patients and the care team as a whole need to be clearly aligned regarding goals. We intend for the FREDOM protocol to be initiated after the patient and his/her healthcare team has together reached a decision that opioid reduction would increase quality of life. The patient may have other specific goals of therapy, such as reduction in opioid side effects, that contribute to overall quality of life and may be independent indicators of success.

### *Starting Dose*

It is common practice at our dispensaries to start patients suffering from pain with a Vireo Yellow product (6:1 THC:CBD; 4.3mg THC and 0.7mg CBD per capsule or per mL of oral solution). Utilization of combination CBD/THC products are essential as the CBD not only potentiates the effect of THC but also mitigates potential side effects.<sup>25</sup> Vireo Health is a proponent of the “start low and go slow” mantra, often commencing CBM with one capsule before bedtime to observe how the medication is tolerated, and in an environment where the patient may be observed by caregivers. If tolerated, patients are able to progress to one capsule twice daily, which provides a relatively steady baseline level of cannabinoids. In addition to the steady effects of oral dosage forms, patients often use faster-acting vaporizers for breakthrough symptoms, as would commonly be seen in non-cannabis-based pain control therapies. This initial regimen of baseline oral medication with patient-titrated vaporizer use has been generally well-tolerated by our patients to date.

We have found that patients vary widely regarding how they respond to new cannabinoid therapies. Generally, we recommend patients carefully monitor their response over a week while they become acclimated. At one week, we encourage patients to fill out the FREDOM Protocol questionnaire electronically, via phone, or in-person at the dispensary. The Patient-Reported Outcome Measures (PROM) collected weekly are vitally important to monitor the patient’s progression through the protocol for both the dispensary and for their primary care team.

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<sup>25</sup> Russo, E. B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology*, 163(7), 1344-1364. doi:10.1111/bph.2011.163

## *Patient-Titrated CBM Dosing*

The baseline patient oral dosing of Vireo Yellow will be complemented as above with Vireo Yellow Vaporizer patient-titrated dosing for breakthrough symptoms. This approach is taken in an effort to maximize potential pain control and minimize CBM-associated side effects related to the rapid onset of vaporized CBM. Vaporized CBMs, which pass directly to the pulmonary vasculature bypassing the first-pass effect, generally reach peak effect within seconds.<sup>26</sup>

## *Initial Opioid Reduction*

We recommend an initial reduction of 20% of the patient's daily opioid dose with implementation of CBM therapy. This initial reduction will bring the patient down from a potentially maximum or near-maximum opioid dose that places the patient at harm for potential overdose, yet poses minimal risk for acute withdrawal symptoms.<sup>27</sup> In the initial phase of the protocol, we are able to focus on the toleration of CBM and adequacy of pain control. As opioids are further weaned in the subsequent weeks, opioid withdrawal symptoms are more likely to enter the clinical picture.

## *Ongoing Opioid Reduction/Discontinuation*

Our aim with the FREDOM protocol is to provide a potential framework by which physicians interact with their patients to decrease opioid use, while using CBM to support pain management. FREDOM is a more gradual reduction of opioids than that found in some existing protocols such as the VA protocol,<sup>28</sup> and we intend a gentle tapering process to maximize patient success. The decision to taper and/or discontinue opioid treatment is a momentous one, and should be formed after a thorough discussion between the patient and care team. We believe that patient willingness is vital to the success of this, or any other, opiate tapering protocol.

Once a decision is made to taper or discontinue therapy, providers can provide guidelines regarding how quickly a patient can taper from opioids, taking into consideration multiple factors such as total opioid dosage and duration to prevent precipitating opioid withdrawal symptoms in physically dependent patients.<sup>29</sup> There is no single tapering strategy to fit all patients; however, reducing overall opioid usage is essential to the protocol goals and CDC directives. An entire field of medicine is dedicated to pain management, so we anticipate

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<sup>26</sup> Grotenhermen, Franjo. "Harm reduction associated with inhalation and oral administration of cannabis and THC." *Journal of Cannabis Therapeutics* 1.3-4 (2001): 133-152.

<sup>27</sup> Fishbain DA, Rosomoff HL, Cutler R. Opiate detoxification protocols: a clinical manual. *Ann Clin Psychiatry*. 1993;5(1):53-65

<sup>28</sup> <http://www.healthquality.va.gov/guidelines/Pain/cot/OpioidTaperingFactSheet23May2013v1.pdf>

<sup>29</sup> Berna, Chantal et al. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain. *Mayo Clinic Proceedings*, Volume 90, Issue 6, 828 - 842

physicians will respond to individual patient characteristics and adjust real-time to symptoms and challenges that arise with individual patients.

Regardless of approach taken by the prescribing physician, clear written and verbal instructions should be given to patients and their families to educate them about the slow taper protocol to minimize withdrawal symptoms or side effects. For patients who are at high risk of engaging in aberrant behaviors (e.g., substance abuse disorder, medication diversion, high psychosocial risk factors), tapering opioids and CBM recommendation in a primary care setting may not be appropriate. The more appropriate cases are likely those with a multifaceted support system and highly motivated patients. Recently, Boenke et al observed that patients in a cannabis dispensaries were able to reduce their total opioid usage by 64% despite suffering from chronic pain.<sup>30</sup> Well-established validated withdrawal scores exist for close monitoring of patients regarding opioid withdrawal symptoms.<sup>31</sup> Nonetheless, certain circumstances don't allow for slow tapering (e.g. allergic reactions, law enforcement) and flexibility is required. It is our hope that CBM can play a significant role in a multi-pronged supportive approach to such situations as well.

### *Data Collection and Analysis*

Vireo Health collects weekly PROM in conjunction with the patient's medical provider. These measures can be obtained electronically, via phone, in person at a Vireo Health dispensary or at the doctor's office.

- 1) Milligrams of morphine equivalents taken per day
- 2) Milligrams of THC and CBD utilized per day, including via patient-titrated vaporizer, validated by amount purchased at dispensaries
- 3) Other medications such as benzodiazepines, sleep medications
- 4) Brief pain inventory, short form
- 5) Quality of life score, short form
- 6) Cannabis side effect score
- 7) Opioid withdrawal score
- 8) Opioid side effect score
- 9) Other qualitative patient-stated goals

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<sup>30</sup> Boehnke, Kevin F. et al. Medical cannabis associated with decreased opiate medication use in retrospective cross-sectional survey of chronic pain patients DOI: <http://dx.doi.org/10.1016/j.jpain.2016.03.002>

<sup>31</sup> Tompkins, D.A., Bigelow, G.E., Harrison, J.A., Johnson, R.E., Fudala, P.J., Strain, E.C. Concurrent validation of the Clinical Opioid Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. (2009) *Drug and Alcohol Dependence*, 105 (1-2), pp. 154-159. doi: 10.1016/j.drugalcdep.2009.07.001

## *Ongoing Monitoring*

Ongoing monitoring is of utmost importance in these patients. FREDOM is not a rigid or proven opioid tapering protocol and ongoing involvement of the patient's primary physician is vital to patient safety and success. Vireo Health is able to make recommendations as to supportive CBM therapy, but opioid discontinuation will be guided by the primary medical care team.

## *Discontinuation of the Protocol*

Cessation of the protocol can occur for several reasons. If the patient does not tolerate CBMs or does not have adequate pain control in the first week of the protocol, we recommend discontinuation at that time. If, as the patient progresses through opioid weaning, the patient pain is no longer controlled, the patient may stop the protocol, back up one dose and maintain with ongoing opioid and CBM therapy.

If at any time the patient, primary physician or Vireo Health feels that there is diversion of CBMs or opioids, the protocol should be stopped. Other contraindications may arise over time, such as pregnancy, which will also mandate protocol discontinuation.

It should be clearly stated that no claims are being made as to the efficacy of cannabis in the treatment of pain or any other medical conditions. FREDOM is simply another potential tool for physicians to consider as part of a patient's comprehensive treatment plan. Medical cannabis and FREDOM have not been evaluated by the FDA or any other regulatory agency.