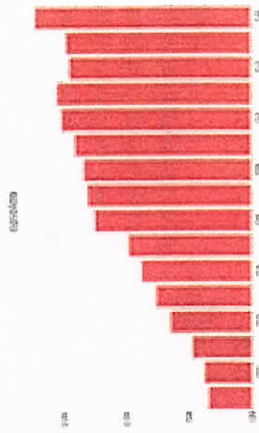


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Research & Policy Background

There is ample evidence to support the concept that opioids could be replaced, in part, by cannabis, for management of pain.

- A February 2016 paper published in the *Clinical Journal of Pain: The Effect of Medicinal Cannabis on Pain and Quality of Life Outcomes in Chronic Pain*, showed a 44% reduction in opioid use in chronic pain patients taking medical cannabis.
- Recently, President Obama announced additional actions to address the prescription opioid abuse and heroin epidemic (*White House Fact Sheet*) and in a February 8, 2016 letter, Senator Elizabeth Warren asked the CDC to explore "the impact of the legalization of medical and recreational marijuana on opioid overdose deaths." As seen in the CDC graph below, opioid overdoses are rising remarkably.



- An October 2014 article in the *Journal of the American Medical Association (Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010)* found that medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Specifically, states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate.
- A July 2015 paper published by the National Bureau of Economic Research (*Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers?*) found that "providing broader access to medical marijuana may have the potential benefit of reducing abuse of highly addictive painkillers."
- A September 2015 article in the *Drug and Alcohol Review (Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors)* found that 80.3% of those surveyed reported substituting cannabis for prescription drugs.



The FREDOM Protocol

(Flexible Reduction and Expedited Discontinuation of Opioid Medications)

A potential path for physicians to help patients struggling with chronic or intractable pain

This first-of-its-kind protocol has been released in draft form as a 'working paper' in order to elicit feedback from the largest possible number of physicians and researchers.

The FREDOM Protocol | Replacing opioids with medical cannabis

FREDOM protocol supportive background:

1. Millions of Americans suffer from pain
2. Opiates are commonly utilized
3. Opioids are associated with fatal overdoses
4. New CDC guidelines encourage limited opioid use and avoidance of long-term use
5. Opiates often fail to relieve symptoms of chronic pain
6. Some studies have shown that cannabis may be effective for pain relief
7. Cannabis is not associated with fatal overdoses
8. In medical cannabis states, overdose deaths have declined.

GOALS:

- Patients will maintain or improve pain and quality of life, while reducing opioids through the use of cannabis-based medicines.
- Replacing opiates with cannabis extracts for pain management will result in fewer fatal opioid overdoses long-term.

In 2014, nearly two million Americans abused or were dependent on prescription pain killers, and more than 14,000 people died as a result of their use, according to the Centers for Disease Control and Prevention (CDC). The number of deaths has quadrupled since 1999. Each day, almost 1,000 Americans are treated in emergency rooms for using these drugs improperly.

Vireo is taking an 'open source' approach to its draft protocol. Over time, Vireo hopes that feedback will contribute to an improved understanding about the extent to which medical cannabis can serve as a viable alternative to opioids.

Vireo is starting observational data collection around the FREDOM protocol this summer.

As of April 2016, Vireo Health's two subsidiaries – Vireo Health of New York and Minnesota Medical Solutions – had access to a population of more than 3,000 patients certified by physicians to use medical cannabis under their respective state laws.

Beginning on August 1, 2016, patients in Minnesota with intractable pain — pain that can't be relieved or cured with other methods — can be certified to use cannabis-based medicine. Many of these patients use opioids on a regular basis and will therefore qualify to participate in the planned observational study. Since New York statute does not currently include pain itself as a qualifying condition, likely fewer patients would be able to participate under current qualifying conditions such as cancer or terminal illness.

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Patient-Reported Outcome Measures:

1. Patient-stated goal
2. Pain level
3. Opiate dose
4. Opiate side effects
5. Cannabis dose
6. Cannabis side effects

