



# the PRUDENT prescriber

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## Cannabis-Based Products for Chronic Pain: Reefer Madness or Real Medicine?

Although opioids are frequently prescribed for chronic pain, a recent review found that these drugs have small to modest effects on pain and function. (Comparative Effectiveness Review, Number 229. Agency for Healthcare Research and Quality; 2020.) With limited benefits, safe alternative pain treatments are needed.

### Is there a role for cannabis in relieving chronic pain?

To date, the FDA has not approved a marketing application for cannabis for the treatment of any disease or condition. The agency has, however, approved one cannabis-derived drug product: Epidiolex for some rare pediatric seizures. Three synthetic cannabis-related drug products: Marinol (dronabinol) and Syndros (dronabinol) are synthetic delta-9- tetrahydrocannabinol (THC) which is considered the psychoactive intoxicating component of cannabis and FDA approved for nausea associated with cancer chemotherapy and for the treatment of anorexia associated with weight loss in AIDS patients. The third drug is Cesamet(nabilone), which has a chemical structure similar to THC that is indicated for the nausea associated with cancer chemotherapy.

Here's a brief look at the science of using cannabis for chronic pain:

1. **McDonagh et al.** (*Ann Intern Med* 2022 June 7) performed a meta-analysis of 18 RCTs (n=1740) and seven cohort studies (n=13,095) that evaluated the benefits and harms of cannabinoids in patients with chronic pain. The studies were primarily short term (1-6 months). 56% of the studies enrolled patients with neuropathic pain. Cannabis products were categorized by delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio, route of administration and source (plant-based, synthetic or extract).

### Results:

Synthetic products (dronabinol, nabilone) with high THC-to-CBD ratios and extracted products with comparable THC-to-CBD ratios (1:1) resulted in moderate improvements in pain severity (0.5-1.0-point reductions on a 10-point scale).

High 1:1 THC to CBD ratio products were associated with significantly more adverse effects, especially dizziness, nausea and sedation.

2. **The European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management** (European Journal of Pain October 2018): Therapy with cannabis-based medicines should only be considered by experienced clinicians as part of a multidisciplinary treatment. The quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for chronic neuropathic pain.
3. **The Role of Cannabis, Cannabidiol and Other Cannabinoids in Chronic Pain. The Perspective of Physicians** [The Journal of Neuroimmune Pharmacology 17, pages 318-333 (2022)] Although conflicting opinions are myriad, the majority of reviews in the past concluded that medical cannabis and cannabinoids *may* have a significant role in the management of pain.
4. **Cheng et al. in Pain Practice September 2022 reviewed 26 studies that reported on healthcare providers viewpoints of utilizing cannabis for pain.** Although a vast majority of clinicians support utilizing cannabis for pain, many involved in managing patients with pain reported being not ready or comfortable in answering patients' questions regarding cannabis, discussing cannabis with patients or other healthcare professionals, or writing a prescription for cannabis.

Common concerns raised by patients pertained to side-effects, legality issues, addiction, physicians' lack of experience with cannabis, and stigma.



- The McDonagh meta-analysis suggests that cannabis products have *a very modest effect on neuropathic pain* in the short term. There was a significant incidence of adverse effects, particularly dizziness and sedation.
- Cannabis is unimpressive as an analgesic for acute pain. Further, the literature review suggests that there's no evidence supporting long-term use of cannabis products for chronic pain.
- The frequency of cannabis dependence among recreational users is frequently cited based on US data as 9%. The addiction risk of therapeutic cannabis usage, in contrast, approaches 0% in formal studies [*Comprehensive Treatment of Chronic Pain by Medical, Interventional and Behavioral Approaches* New York Springer 2013]
- There is little information on other harms of using cannabis for pain: psychosis, cognitive impairment, drug-drug interactions.
- Whatever your take on cannabis for pain, it is certain that some of your patients, will do their own "n of 1" study.
- Clinicians should be prepared to discuss benefits and risks of medical cannabis products for short term management of chronic pain.

### Whither Paxlovid?

As I create this newsletter in late May 2023, the United States continues to experience ~120 deaths per day from Covid-19. Happily, that number is down from 250-300 daily deaths in late April 2023. While the CDC

has approved an additional Covid bivalent booster for those who are immunocompromised or over 50, only 17% of eligible adults have received an initial booster dose.

Covid hospitalizations and deaths are decreasing, but there is still a significant proportion of our country fiercely anti-vax and un- or under-immunized. We do not have a good handle on the percentage of this population who have garnered immunity from infection.

Initial studies of Paxlovid were done on unvaccinated patients during the Delta wave of the pandemic. The number needed to prevent one hospitalization/death in those studies was 18. (N Engl J Med 2022; 386:1397)

In January 2023, unpublished data from Pfizer (manufacturer of Paxlovid) suggested that the drug had no significant effect on hospitalization or death in immunized healthy people under 65 years of age. The same data revealed that Paxlovid had a modest effect in preventing hospitalization and death in immunized patient 75 years and older. NNI = 80-100.

In January 2023, Dryden-Peterson et al. looked at the effectiveness of Paxlovid in more heavily immunized populations. (Ann Intern Med 2023 Jan; 176:77) In this retrospective cohort study that looked at 45,000 patients. Age >50 years, 90% had received at least 3 doses of vaccine. Of the 28% of the cohort who received Paxlovid, hospitalization/death occurred in 0.55% of the group, while hospitalization/death occurred in 0.97% of the untreated group. NNT to prevent one hospitalization/death in this cohort= 212.

There are data from a cohort study of 281,793 veterans with Covid-19 and at least one risk factor for progression to severe Covid-19 illness that suggest that taking Paxlovid, compared with placebo, for an acute Covid infection is associated with a decreased incidence of Long Covid. NNT=22. (JAMA Intern Med 2023 March 23)



- Paxlovid is still free.
- It may decrease the incidence of long Covid.
- My geriatrician/internist daughter-in-law, whom I trust implicitly, is no longer prescribing Paxlovid to her elderly, frail nursing home patients who are mostly immunized.
- The side effect profile is benign but unpleasant at times (metallic taste and diarrhea).
- Is there a role for Paxlovid in the unimmunized patient with no recent documented COVID infection?

### **Opill: First OTC Oral Contraceptive in the Works?**

On May 18, 2023, an Advisory Committee to the FDA unanimously endorsed making a birth control pill available without a prescription. In 2014 HRA Pharma bought the rights to Opill and has been lobbying for almost a decade to bring this progesterone only pill (norgestrel) to the OTC market. Despite some concerns from the FDA staff regarding HRA's testing of Opill (questioning whether patients could understand the instructions and too few adolescents in the studies) the committee voted 17-0 to recommend approval to the FDA. If approved and it is likely in late summer or early fall, the United States would join 100 other countries that already allow OTC purchase of birth control pills.



Over half of pregnancies in the United States are unintended. That percentage is even higher among adolescents. As the barriers to abortion in the United States grow bigger by the day, the availability of birth control pills over the counter is a significant advance in women's reproductive rights.

### TB or Not TB: What Sayeth Thou J&J?

Epidemiologist Tom Orr's poetry last month reminded us that tuberculosis is still with us. Worldwide, 1.5 million people still die each year of tuberculosis which is more than those who die of homicide, malaria and war combined. In 2012, bedaquiline was brought to market largely through local governments' funding in multiple countries. Bedaquiline has become a critical component in treating multidrug-resistant tuberculosis (MDR-TB). The drug is now owned and distributed entirely by Johnson and Johnson (J&J). Its patent expires in July 2023. Guess what? J&J is now attempting to create secondary patents that will keep this vitally important drug in their financial stable. J&J prices bedaquiline at \$1.50 per day (\$272 for a six-month treatment regimen). With generic competition the price should drop to about 50 cents a day where bedaquiline could still be profitable for manufacturers and markedly increase its availability.



C'mon J&J do the responsible thing!

"No one should approach the temple of science with the soul of a money changer."  
-Thomas Browne, 1640

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