Pain Medicine: Perspective and Practice
Cannabis for Pain and Substantiating the Evidence
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Dr. Abrams spoke at the 2017 Family Medicine Clinical Forum on Cannabis: What Family Physicians Need to Know. The PDF of his presentation is available here. This article appears in the June 2017 issue of San Francisco Marin Medicine and is reprinted with the permission of the San Francisco and Marin Medical Society.

Surveys of patients accessing cannabis for medical use have consistently demonstrated that chronic pain is the most frequently listed condition for which people are seeking treatment.¹ ² State registries also generally support this finding, although ironically there are some states that do not allow chronic pain as an eligible condition for which cannabis can be recommended. It has been postulated that the main reason that we and other species have cannabinoid receptors and endogenous cannabinoids (endocannabinoids) is to help us modulate the body’s response to pain. Local clinicians caring for patients who have access to medicinal cannabis over the past twenty-one years have likely been impressed with the pain-relieving effects they have appreciated. What does the research say? The Institute of Medicine listed pain as one of the conditions that may benefit from cannabis in their 1999 report, Marijuana and Medicine. More recently, the National Academies of Sciences, Engineering and Medicine (NASEM) conducted a rapid turnaround review of The Health Effects of Cannabis and Cannabinoids to update the earlier study.

The report was issued in January 2017.³ As a result of the November 2016 elections, medicinal cannabis is now legal in 28 states and the District of Columbia.⁴ In anticipation of these ballot results, a consortium of sponsors commissioned the NASEM to develop a comprehensive, in-depth review of the existing evidence regarding the health effects of cannabis and cannabinoids. In addition, NASEM was asked to make recommendations regarding a research agenda.
The 16-member committee, first convened in June 2016, adopted key features of a systematic review process and evaluated meta-analyses and systematic reviews published between 2011-2016 that investigated both the beneficial and harmful health effects of cannabis and cannabinoids. If no high quality systematic reviews had been published regarding the eleven prioritized health endpoints, results of high quality primary research published since 1999 were included. The report priorities included therapeutic effects and potential adverse effects in areas such as cancer incidence; cardiometabolic risk; respiratory disease; immune function; injury and death; prenatal, perinatal and postnatal outcomes; psychosocial outcomes; mental health; problem cannabis use; and cannabis use and abuse of other substances.

Of the 24 therapeutic areas identified, conclusive research evidence was identified in only two: 1) oral cannabinoids are effective anti-emetics in adults with chemotherapy- induced nausea and vomiting, 2) short-term use of oral cannabinoids improves patient-reported spasticity symptoms in adults with multiple sclerosis. This conclusion is drawn when strong effectiveness of the treatment for the health endpoint of interest and there are many supportive findings from good-quality studies with no credible opposing findings. The report concluded that there is substantial evidence (strong evidence but few credible opposing findings) that cannabis is an effective treatment for chronic pain in adults. Five good- to fair-quality systematic reviews and two primary literature articles were identified assessing the effects of cannabinoids on pain. Thus, in total, 28 pain trials were included in the review; 17 of these investigated cannabinoids in peripheral neuropathy pain. Information regarding the effectiveness of cannabis or cannabinoids in other painful conditions is limited.

Most of the chronic pain studies reviewed were short-term and with small sample sizes limiting the assessment of long-term effects. Chronic pain was the only therapeutic area where there was a small body of evidence supporting the benefits of botanical cannabis and not just the isolated cannabinoid delta-9-tetrahydrocannabinol in its pharmaceutical preparations. No studies of the higher potency oral products available from many dispensaries nationwide have yet been conducted as the only legal source of cannabis for investigation continues to be the National Institute on Drug Abuse (NIDA). Contributing to the lack of research findings on the effectiveness of cannabis are the significant barriers to research of Schedule I substance. This
becomes increasingly problematic as the momentum gains for both legalization of medical and recreational cannabis.

Based on the existing evidence, cannabis may be considered prior to initiating opioid therapies in patients with neuropathy and other chronic pain syndromes. Early evidence is promising as states where medical cannabis is legal have reported decreases in opiate prescriptions and opiate-related mortality. Animal models and a small human study support decreased pain with no adverse pharmacokinetic interactions between vaporized cannabis and sustained-release opiate analgesics. In view of the current significant opiate epidemic, using cannabis instead of opiates for chronic pain and/or to allow opiate-dependent patients to attempt to wean off of their narcotics may be a feasible harm-reduction intervention.

One question that remains unanswered is the effect of other cannabinoids on pain. Cannabidiol (CBD) has been catapulted to the forefront of attention as perhaps the new most-favored cannabinoid because it lacks the “high” associated with delta-9-tetrahydrocannabinol. Many patients seeking relief from pain are not enthusiastic about the mind-altering effects of tetrahydro-cannabinol (THC). With the knowledge that cannabidiol is anti-inflammatory and analgesic in animal models, more patients are trying products with varying ratios of CBD:THC for pain relief.

Clinicians may find that they are frequently queried about what is the correct ratio for pain management. Again, there is no answer because there is no data. The ongoing study at Zuckerberg San Francisco General Hospital investigating a 5%THC:5%CBD vaporized cannabis in sickle cell patient appears to be the first trial in the US investigating an inhaled THC:CBD strain. That is not to say that patients are not benefiting from using CBD-containing products; it is just that the plural of anecdote is still not evidence.

Another issue that remains unclear is what is the best mode of delivery for pain relief? When inhaled—smoked or vaporized—the peak plasma concentration of THC is reached in minutes and declines rapidly. When taken by mouth as edibles, capsules, tincture or oils, the peak plasma concentration can occur as late as two and a half hours after ingestion with a terminal half-life of 20-to-30 hours. When ingested orally, first past metabolism in the liver converts the delta-9-THC into another psychoactive metabolite: 11-OH-THC. This is why people generally get a more deep and prolonged psychoactive effect with oral routes of administration. The pharmacokinetic profile of sublingual preparations available in dispensaries is likely somewhere between inhaled and ingested cannabis but the only available evidence stems from studies of the pharmaceutical whole plant extract, nabiximols, licensed and available in Canada and much of the European Union but not yet in the US. There may be some populations in which
cannabis as an analgesic should be approached with caution if at all. The NASEM report suggests that cannabis is not indicated before the central nervous system is fully programmed and developed at age 25. Certainly many Baby Boomers attending college in the 1960s found 18 to be a convenient age to begin to experiment with recreational cannabis and appear to be none the worse for the experience. Children and adolescents, however, may not be appropriate candidates for initiation of cannabis as an analgesic. A growing body of research is being built on cannabinoid medicines utilized as anti-seizure medications in refractory childhood epilepsies and anecdotal reports of pediatricians finding benefit from the use of oral cannabis-based analgesics, particularly CBD products, but, in general, alternatives should be investigated first.

Older seniors constitute another clinical population in which cannabis as an analgesic should be considered with caution. As cannabis can both elevate and lower blood pressure while increasing heart rate, cardiovascular stress is an issue. Postural hypotension and risk of falling with an obvious potential for fracture would also be a significant concern. Seniors may also be more averse to inhalation as a mode of delivery and need to be apprised clearly of the delayed onset of edible and oral preparations to avoid excessive dosing.

Currently, we hear significant political rhetoric about the role of cannabis in therapeutic care. As the NASEM report outlines, we need further high-quality evidence to understand the health risks and therapeutic benefits associated with cannabis. Hopefully further evidence will support individual patient and care provider conversations, advocacy for public health measures, and the development of sound, evidence-informed policy and practice.

References

6. Bachhuber MA, Saloner B, Cunningham CO. Medical Cannabis Laws and Opioid Analgesic


Donald Abrams is chief of Hematology-Oncology at Zuckerberg San Francisco General and a Professor of Clinical Medicine at the University of California San Francisco. He has been conducting research with cannabis since 1996. He was a member of the sixteen-member committee of the National Academies of Sciences, Engineering and Medicine which issued the report on The Health Effects of Cannabis and Cannabinoids in January 2017.