Cannabis in Pain and Palliative Care

By DONALD I. ABRAMS, MD

History of the Medical Use of Cannabis

Cannabis is one of the oldest known psychoactive plants. The 2700-year-old tomb of a Caucasian shaman excavated in Northern China contained 2 clay pots with flowers from the female cannabis plant (1). This suggests that cannabis was used as medicine or in religious ceremonies in China long ago. Cannabis then migrated from China to the Indian subcontinent, where it was first introduced into Western medicine in the 1840s by W.B. O'Shaughnessy, a surgeon for the British East Indies Company. O'Shaughnessy brought cannabis to the United Kingdom, where it reportedly became Queen Victoria's favorite treatment for menstrual cramps. It was known for its sedative, analgesic, and anti-inflammatory effects. In the early 1900s, most of the manufacturers in the United States of what we now recognize as pharmaceuticals had their own preparations of cannabis medicines. However, physician interest in cannabis began to decline as therapies were developed that spoke to each of the individual indications of cannabis.

The real death knell was the introduction of the Marihuana Tax Act in 1937, which was pushed through Congress by Harry Anslinger, a prohibitionist who became the first head of the Federal Narcotics Bureau. He believed that increased use of cannabis by African American jazz musicians and migrant workers from Latin America would lead to increased crime and mental illness in the United States. The Act imposed a tax of $1 per ounce for medical use and $100 per ounce for recreational use of cannabis, which was significant in 1937 dollars.

Interestingly, the American Medical Association was virtually alone in opposing the Act because it felt there was no real evidence the drug was dangerous and the Act would impede future clinical investigation. Cannabis was removed from the US pharmacopeia in 1942.

Also in 1942, Fiorello LaGuardia, the mayor of New York City, asked a group of august scientists to evaluate whether the use of cannabis would lead to increased mental illness and crime. The LaGuardia Commission concluded that the claim was not true. Every 10 years since, the government commissions a body to investigate cannabis as medicine. We are a little off schedule, though, since the last report was the 1999 Institute of Medicine (IOM) report, Marijuana as Medicine. Although these reviews have reported that cannabis is safe and has some medical benefit, these findings are largely ignored.

In fact, the Controlled Substance Act in 1970 classified cannabis as a Schedule I drug with a high potential for abuse and no accepted medical use. This would seem to contradict the findings of the 1999 IOM report, which concluded that cannabis is useful for anorexia, nausea, and pain.

Components of Cannabis

The main psychoactive component of cannabis is delta-9-THC, which, as the shaman recognized, is present in the resin exuded from the flowers of the female plants. There are at least 70 other cannabinoids in the plant. These 21-carbon terpenophenolic compounds probably also have biologic activity. For example, delta-8-THC has been studied as an antiemetic for children with cancer receiving chemotherapy in Israel and was found to be as effective as delta-9-THC (2). Cannabidiol (CBD) is becoming more widely recognized as a potent anti-inflammatory and analgesic that does not have the psychoactive effects of delta-9-THC. Other noncannabinoid components of cannabis may also have beneficial effects, including terpenoids and flavonoids, which are probably very important for blood flow and anti-inflammatory activity.

Two synthetic preparations of delta-9-THC, dronabinol and nabilone, are licensed and approved for the treatment of nausea and anorexia. However, these agents lack the other balancing chemicals in the plant that boost the beneficial effects and temper some of the adverse effects (AEs) of delta-9-THC, providing the sort of yin and yang that leads traditional Chinese medicine practitioners to prefer using the whole plant as opposed to extracting the single active moiety.

Cannabinoid Receptors

Although there has not been a great deal of research on the use of medicinal cannabis in the last 60 years, we have made progress in understanding the system that allows us to respond to the plant cannabinoid, the phytocannabinoid.

Two receptors have been identified in animals, the CB_1 receptor and the CB_2 receptor, which are G-proteins coupled to inhibiting adenylyl cyclase. The central nervous system responses are largely mediated by way of the CB_1 receptor. Activation of the CB_1 receptor inhibits N-type voltage-gated Ca channels and increases both K conductance in hippocampal neurons and prostaglandin production.

The endocannabinoids complex with the CB_1 receptor and, after inducing transmembrane activity, they may be involved in appetite control, immune function, muscle control, pain, intraocular pressure, cognition, emesis, neuroexcitability, reward, and thermoregulation.

The largest concentrations of the CB_1 receptor are found in the basal ganglia, cerebellum, and areas related to reward. The CB_2 receptor was initially detected in immune system cells—macrophages, the marginal zone of the spleen, B lymphocytes of the peripheral blood, and the natural killer cells—suggesting that there may be some activity related to immunity. It was originally thought that the CB_2 receptor was not expressed in the brain, but this is not true, although it is present at a much lower level than the CB_1 receptor. In addition to its role in immunity, the CB_2 receptor is also involved in cell proliferation, inflammation, and pain. It is believed that there may be other cannabinoid receptors yet to be identified that may also have a role in modulation of pain.

So, why do we have these receptors? Just as we know that the body makes endogenous opioids (endorphins), it also makes its own cannabinoids, known as endocannabinoids. The first was named anandamide after the Sanskrit word for "bliss." Other endocannabinoids have been identified, but the 2 that are most commonly felt to be of importance are anandamide and 2-arachidonyl-glycerol. These are produced on demand and then hydrolyzed by fatty acid amide hydrolase (FAAH). The endocannabinoids complex with the CB_1 receptor and, after inducing transmembrane activity, they may be involved in appetite control, immune function, muscle control, pain, intraocular pressure, cognition, emesis, neuroexcitability, reward, and thermoregulation.

What happens if you don't have these receptors? CB_1 knockout mice have increased anxiety and susceptibility to the depressive effects of chronic stress (3); reduced responsiveness to rewarding stimuli (4); significant reduction in feeding and pronounced weight loss (5); and impairment in extinction of aversive memories (6).

Elevated levels of the CB_1 receptor, like opioid receptors, are found in areas of the brain that modulate nocioceptive processing. The CB_1 and CB_2 agonists also have peripheral analgesic actions and probably exert anti-inflammatory effects. Although the data are somewhat conflicting, the analgesic effects of cannabinoids are not blocked by opioid antagonists. In a cancer trial, oral THC 20 mg was thought to be comparable to codeine 120 mg, but with more marked psychological effects (7).

Cannabinoids in Neuropathic Pain

HIV-related peripheral neuropathy

HIV-related neuropathy, a painful distal symmetric polyneuropathy, is very difficult to treat. Opioids are ineffective and gabapentin, which is frequently used, may interact with other medications. Patients have, however, reported anecdotal benefit from cannabis. Since cannabinoids were effective in a rat model of neuropathic pain (NP) (8), we conducted a study of cannabis in painful HIV-associated sensory neuropathy. We started the study by doing an open-label intervention in 16 patients with HIV-related peripheral neuropathy to determine whether there was a treatment effect. We used the effect size to calculate the dose for a follow-up, placebo-controlled trial to investigate the analgesic effects of smoked cannabis on both the clinical NP and experimental pain models (9).

Our primary outcome measures in this study were the effect on NP, which we evaluated by having subjects complete a daily pain diary, as well as the effect immediately before and after smoking the first and last cannabis cigarettes in the clinical trial. On the first and last days, we also assessed experimentally induced secondary hyperalgesia. My colleagues in the University of California–San Francisco Pain Clinical Research Center like to see patients who have >20% reduction in their pain when evaluating a new drug as an analgesic, but since we were dealing with cannabis, which is so controversial, they believed we should count responders as individuals who experience a >30% reduction in their pain.

Our study included HIV patients who had peripheral neuropathy—related either to the virus itself, to the drugs used to treat it, or both—and who entered with an average daily pain score of ≥30/100. Like all other clinical trials we conduct on cannabis, we selected patients who had inhaled cannabis at least 6 times in their lives, so we did not have to teach them how to inhale and so they knew the potential psychoactive effects. We ultimately randomized 55 patients and determined that we would need 50 patients enrolled to see a difference between those who were smoking cannabis and those who were smoking placebo cannabis, a substance from which we had extracted the cannabinoids but still had flavonoids and terpenoids, so it smelled and looked like cannabis. All patients used the Foltin puff procedure to standardize inhalation.

Enrolled patients had long-standing, well-controlled HIV. Viral loads were undetectable, and CD4 cell counts were quite good. The average duration of NP at entry was 6 years, and baseline pain scores were about 50/100. Some patients were taking medications that included gabapentin, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Pain in the placebo group declined slightly in the first week, but by the time the study was over, it was generally the same as baseline scores. In the cannabis group, however, we saw a marked decrease in pain that persisted throughout the clinical trial. The percentage of patients achieving a >30% reduction in pain was 52% in the cannabis group, compared to 24% in the placebo group. Similarly, the cannabis group experienced a 72% pain reduction after smoking the first cigarette versus a 15% reduction in the placebo group. Finally, the area of secondary hyperalgesia (experimental pain model) did not change in the placebo group but did decline in the cannabis group. We concluded that smoked cannabis is an effective treatment in patients with painful HIV-related peripheral neuropathy and is also effective in attenuating central sensitization produced by a standardized experimental pain model. The number needed to treat (NNT) in our study was 3.6, which is comparable to the NNT of gabapentin in other peripheral NP syndromes (10,11).

Other Neuropathic Pain Conditions

We do not know if cannabis is effective in diabetic peripheral NP. A Ware et al study looked at a single-dose inhalation of various strengths of cannabis in other NP conditions and found results similar to those we reported—with a high-dose THC preparation, significant pain relief was achieved compared to placebo (12).

I have been very interested in studying chemotherapy-related peripheral neuropathy, which is a big problem for me as an oncologist. I can cure many patients of their cancer, but they are disabled because they have NP. However, cancer patients have been difficult to enroll in cannabis trials, so I have not done a study.

Cannabis and Opioids

Opioids and cannabinoids share several pharmacologic properties, and they were initially thought to act on the same pathways to produce their pharmacologic actions. Cannabinoids interact with the kappa and delta receptors to produce pain relief, while opioid analgesia is more generally mediated by the mu receptors, but they may be enhanced by the cannabinoid effects. So, the cannabinoid-opioid interaction may occur at the level of their signal transduction mechanisms. This is quite an exciting field—cannabinoids can potentiate the analgesic effects of opioids, as demonstrated in mice and rats. THC greatly enhances the analgesic effect of morphine in a synergistic fashion, and the increased potency of other mu opioids has been demonstrated (13-15).

Morphine is metabolized by glucuronidation. In the following study we asked (D. I. A., unpublished data, 2010) whether cannabis, delivered via vaporization, accelerates glucuronidation. If so, morphine levels might be lower. In a capsule form, oral THC delays gastric emptying, so if vaporized cannabis does the same, the time course of morphine absorption may be altered. We also wanted to look at the interaction between cannabinoids and oxycodone. Oxycodone is metabolized in the liver by the CYP450, isoform 2D6 and also undergoes glucuronidation. If vaporized cannabis affects CYP450 or glucuronidation, oxycodone levels may also change, and the time course of absorption may be altered.

The entry criteria included participants with all types of pain, including musculoskeletal pain syndromes, posttraumatic pain, and arthritis. We are still evaluating the data, but it appears that after exposure to 5 days of cannabis, plasma levels of both morphine and oxycodone are unchanged or perhaps slightly decreased. We would then hypothesize that pain might increase in these patients; but if you look at the overall cohort, the average pain was reduced about 25%, which was statistically significant.

I have found that pain physicians often do not prescribe opioids or withhold opioids from patients who test positive for cannabis in their urine, which is

unfortunate because these patients have seemingly discovered that coadministration of cannabinoids boosts the effect of their opioids and perhaps allows them to take lower dosages for prolonged periods of time.

Therapeutic Value and Safety

The1999 IOM report indicated a potential therapeutic value for cannabinoid drugs in pain relief, control of nausea and vomiting, and appetite stimulation. It also concluded that the effects of isolated THC are best established; that the effects of cannabinoids are generally modest; and that there are usually more effective medications. However, as an oncologist, I frequently see patients who suffer from anorexia, nausea, pain (despite taking opioids), insomnia, and depression. Rather than writing them prescriptions for 5 different medications, all of which have potential toxicity, AEs, and addictive potential, I can recommend just cannabis.

What about the safety of cannabis? No deaths have been reported from overdose of cannabis. An estimated 800 cigarettes are required to kill, and that death is secondary to carbon monoxide, not cannabinoid poisoning. Also, the addictive potential is lower than that of caffeine. Withdrawal is also tempered by the fact that cannabis is stored in fat, so there is no precipitous drop in the blood level if a person stops suddenly (16).

I do not believe there are significant carcinogenic agents in cannabis. Donald Tashkin, MD, a pulmonologist at UCLA, has done the bulk of work in the last 30 years to determine the pulmonary AEs of smoking cannabis. His group conducted a large case-controlled study in Los Angeles of 1200 patients with lung cancer and found that those who smoked cannabis regularly had a 26% reduction in the risk of lung cancer (17), possibly because of the anti-inflammatories and antioxidants in the plant. Also, people do not generally smoke 2 packs of cannabis joints a day, so it is not the same as nicotine cigarettes.

The IOM report also stated that that the goal of clinical trials of smoked cannabis would be the development of smokeless, rapid-onset cannabinoid delivery system. That may take many years, and in the meantime patients with debilitating symptoms may find relief in smoked cannabis or marijuana.

Vaporization

With funding from the University of California's Center for Medicinal Cannabis Research, we investigated a potential smokeless delivery system: a vaporizer (18). This device is basically a heating element with a fan. The cannabis is put into a chamber, and then a valve is attached. THC vaporizes at a lower temperature than that at which it burns, and the vapors are cooler, purer, and probably less toxic. They may also have more psychoactive activity and potency because less of the THC content is burned off.

This is probably the easiest study I have conducted. We looked for healthy, chronic marijuana smokers aged 25 to 40 for a 6-day inpatient study. On each of the 6 days, they either smoked or vaporized half of a cigarette at 3 different THC dosages (1.7%, 3.4%, and 6.8%). We looked for the level of cannabinoids in their bloodstream as well as expired carbon monoxide, which is a measure of exposure to noxious gases.

The plasma cannabinoid levels were the same in both groups. The group that smoked had an increase in expired carbon monoxide, but the vaporization group did not. Therefore, we concluded that vaporization of cannabis is safe and effective. The plasma THC levels and physiologic effects (subjective "high") were comparable, and expired carbon monoxide was not increased. Participants also had a clear preference for vaporization over smoking, and it could be used as a delivery system in clinical effectiveness trials.

Dosing

One of the primary concerns is effective dosing. There is no standardization, as is the case with any botanical. It is also difficult to standardize a dose of inhaled medicine. Patient variation—setting, prior experience, pharmacogenomics—is also an issue.

In 2004, my colleagues and I concluded that a patient-determined, self-dosing model was best (19). Although it is not unheard of that people can self-titrate with medication, it took a few years after the marijuana law was passed for the Medical Board of California to reassure physicians that if they use proper care in recommending medical marijuana to their patients, their activity will be viewed the same as prescribing any other appropriate medical intervention (20).

It is important to note that when marijuana is inhaled, the cannabinoids reach a peak plasma concentration in 2.5 minutes that declines quickly over 30 minutes. Eating cannabis products or taking oral dronabinol produces a much lower peak level, which is reached in 2.5 hours. The terminal half-life is also 25 hours, so I do not recommend ingestion for people who want rapid effect and rapid titration. In addition, when

taken by mouth, first-pass metabolism generates an 11-OH-THC, which is a psychoactive metabolite that is produced in lower quantities when marijuana is inhaled.

Public Acceptance

A Lou Dobbs poll in 2005 asked Americans (n=4638) if the federal government should prosecute physicians who prescribe medical marijuana; 94% responded no and 6% responded yes (21). Recent national surveys have also found that nearly 75% of respondents believe that patients should have access to marijuana for medical purposes, and an equal percentage of physicians agree (22). Right now, 14 states and Washington, DC have legislation that permits physicians to discuss cannabis use with patients, and more are considering it. ■

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