

Cannabis-Based Medicine: Why is it Such a Conundrum?

By Alice P. Mead, J.D.

Ms. Mead served as staff counsel to the California Medical Association for 11 years, focusing on bioethics, including informed consent, confidentiality, end-of-life care, discrimination, and drug abuse treatment/control issues. Ms. Mead currently works as a consultant, specializing in regulatory law governing new drug and device development; patient confidentiality and informed consent; and domestic and international treaty issues relating to controlled drugs and drug treatment policy. Her clients include members of the pharmaceutical industry and other health-related organizations.

Cannabinoids. Many would call this the “hot new topic” in analgesic research. However, the results of clinical studies with oral tetrahydrocannabinol (THC) are uneven and confusing, and the use of crude herbal cannabis is laden with prejudice and political baggage. Is this, indeed, a promising new area of medication development?

Why Didn't Cannabinoid Medicines Develop in Parallel with the Opiates?

Why have cannabinoids only now come to the attention of the medical and scientific communities? To address that question, we must first take a quick tour through history. In the mid-1800s, through the writings of British physicians such as William O'Shaughnessy and U. Russell Reynolds, Western medicine learned of the therapeutic potential of the cannabis plant. Initially, individual pharmacists compounded oral tinctures and extracts, but, as pharmaceutical companies burgeoned, these manufacturers made such products more broadly available. At a time when therapeutic options were limited, physicians welcomed another potential tool to alleviate suffering.

Earlier in that century, the active analgesic ingredients in opium—morphine and codeine—had been discovered and isolated. Standardized opiates and, later, synthetic medicines were developed. These medications were water soluble, easy to formulate and administer, and had a predictable onset of action. Opium was not smoked for medical purposes; rather it was viewed strictly as an intoxicant. There was a clear distinction between smoked opium and pharmaceutical opioid dosage forms.

What happened to cannabis medicines? Cannabinoids are sticky, highly lipophilic (not water soluble), and THC in particular is unstable unless properly stored or treated. Scientists could not identify the active ingredient(s) of cannabis medicines, and therefore pharmaceutical companies and pharmacists could not prepare adequately standardized products. Moreover,

patient response was variable and unpredictable. Thus, as more “modern” medicines came on the market, cannabis tinctures and extracts began to fall out of favor with the medical profession. At that same time, smoked (recreational) cannabis entered the U.S. and rapidly became demonized by state and federal governments. During hearings on the Marijuana Tax Act of 1937, which imposed onerous administrative burdens on physicians who prescribed cannabis-based products, the AMA voiced merely a weak objection.

Although THC, the primary psychoactive cannabinoid, was discovered and synthesized in 1964, follow-up research was not extensive. Not until the 1970s, when smoked cannabis use increased, were the therapeutic properties of cannabis inadvertently rediscovered by numerous users. Hence, the use of crude, smoked cannabis as “medicine” became entwined with the form used for recreational purposes. However, had technology made it possible to analyze, research, formulate, and deliver cannabinoids as effectively as the opiates, **we might not have a “medical marijuana” debate today.** This vitriolic controversy is merely an artifact of the delayed development path that cannabinoid medicines have followed.

Beginning around 1990, science took a huge leap forward. The endocannabinoid system was discovered, and several endocannabinoid ligands were identified. With a greater understanding of the mechanism of action, researchers rushed to explore the potential of this receptor system. A new era of discovery was born. The resulting body of preclinical studies demonstrates that cannabinoids have analgesic properties (alongside many other potential therapeutic effects) and can affect a wide range of bodily processes and systems. Three categories of cannabinoids have been established: 1) endocannabinoids, which are produced by the body; they are quickly metabolized and, consequently—due to this and the difficulty in patenting endogenous biochemicals—have not yet been studied in humans; 2) phyto-cannabinoids, which are found exclusively in the cannabis plant; and 3) synthetic cannabinoids, which may be synthetic versions of naturally occurring cannabinoids or molecules that are quite novel in structure.

What Have We Learned about the Formulation and Delivery of Cannabis and Cannabinoids?

Particularly with cannabinoids, the delivery system is critically important in order to achieve an acceptable risk/benefit profile. First, oral delivery methods are problematic, unlike with many opiates. Bioavailability is low and patient response is variable. When consumed orally, THC undergoes first pass metabolism by the liver, producing a psychoactive metabolite, 11-hydroxy-THC, which some believe is even more potent than THC. The onset of action is two to four hours, which makes it impossible for patients to titrate their dose

Cannabis-Based Medicine (cont'd)

effectively. Furthermore, when the dose does take effect, it can cause a significant degree of psychoactivity—often of a dysphoric, rather than euphoric, nature. Undesirable side effects, therefore, may prevent a patient from taking a dose that might optimize the therapeutic effect.

By contrast, inhaled cannabinoids—smoked or inhaled cannabis plant material or inhaled synthetic THC—have an almost immediate onset of action. THC blood levels rise dramatically and then decline sharply. This spike has been shown to produce concomitantly significant levels of psychoactivity. Because rapid escalation in blood levels is a hallmark of drugs of abuse, this effect may enhance the risk of abuse potential.

These considerations pose a development challenge: how to provide an adequate therapeutic dose of cannabinoids without incurring unacceptable CNS side effects and/or undue abuse potential? Perhaps patients with chronic conditions would be benefited by an intermediate onset delivery system—one that has an onset of action that is sufficiently rapid to enable them to titrate their dose to remain within the therapeutic window but does not flood the brain and bloodstream with THC. Flexible dosing regimens might help overcome variable interpatient responses.

Second, formulation issues are also challenging and complex. The therapeutic action of cannabinoids does not result from THC alone. THC has analgesic and other therapeutic properties, but it also has significant side effects. Cannabidiol (CBD) is a nonpsychoactive cannabinoid that mitigates the adverse side effects of THC, including its psychoactive effects. Moreover, CBD has independent therapeutic potential, with antiinflammatory, analgesic, anticonvulsant, anti-psychotic, and neuroprotective effects. In ancient times, when cannabis preparations were used medicinally, a field of wild cannabis might have yielded approximately 50:50 THC/CBD. However, North American cannabis contains almost exclusively THC, having been bred to maximize its potency as an intoxicant. Current FDA-approved pharmaceutical products are composed of pure synthetic THC or a THC-analogue. Perhaps restoring CBD in varying ratios will improve the risk/benefit balance for many medical conditions.

Quality is a final, but pivotal, factor in the development of a cannabis-based medicine. Lack of both quality-control and standardization will likely preclude both FDA approval, and widespread physician acceptance, of smoked and other crude herbal cannabis products. As noted above, oral cannabis extracts and tinctures in the early 20th century lacked predictability/reliability of effect. While some of this was no doubt due to the delivery form, the lack of standardization was also problematic. “Medical marijuana” products of today wholly lack the standardization of composition and dose that are the benchmarks of a modern medicine. Moreover, herbal cannabis products

Cannabis-Based Medicine (cont'd)

available in dispensaries may be contaminated by microbes, heavy metals, or pesticides. In addition, physicians who recommend the use of such products lack the data and information necessary to conduct a meaningful informed-consent discussion with patients.

What Might the Future Hold for Cannabis-Based Medicines?

Would the FDA approve a medication that is derived from a complex botanical extract? It is true that most “modern” medicines comprise a synthetic, single-entity active ingredient. However, this is not the *sine qua non* of a modern prescription medicine; rather, such medicines are defined by standardization, reproducibility batch-to-batch, stability and noncontamination. Technology now makes it possible to achieve those goals with botanically based products, and interest in the concept is growing. Recently, the FDA issued a guidance document entitled “Botanical Drug Products.” The document acknowledges that modern pharmaceutical medicines can be derived from botanical materials. However, while somewhat relaxing the requirements of the early developmental stages, the Guidance makes it clear that, by late stage clinical trials and new drug approval (NDA) application, the product must be highly standardized and tested in accordance with all other pharmaceutical standards.

What, then, would be the process for developing a cannabis-derived medicine? Recent research out of the United Kingdom provides one example. At the outset, quality should be built into the botanical starting materials—in this case, the cannabis plant. The cannabis strains must be carefully bred and selected for cannabinoid content and other characteristics. Propagation by cuttings (clones), rather than seeds, is necessary to maintain the integrity and consistency of the plant’s genetics and chemical content. Cultivation should take place in computer-controlled greenhouses where every aspect of the growth cycle can be strictly regulated. Quality control procedures must be incorporated into each stage of the manufacturing process, from harvesting and storage, through decarboxylation, extraction, and final formulation into an appropriate dosage form.

The initial product resulting from the U.K. program—Sativex[®]—is novel both in formulation and in delivery system. The product is delivered as a precisely-metered oromucosal spray. This dosage form, which delivers 100 microliters of medicine, has an intermediate onset of action of 15 to 40 minutes—neither as immediate an effect as inhaled/vaporized cannabinoids, nor as delayed and unpredictable as oral. (Blood levels continue a modest rise, peaking at two to three hours.) This is rapid enough to allow patients with chronic conditions to learn to adjust their individual dose patterns predictably to achieve symptom relief without notable intoxication. The composition is a 1:1 formulation of

Cannabis-Based Medicine (cont'd)

THC/CBD (achieved by mixing a predominantly-THC extract with a predominantly-CBD extract). This ratio appears to improve efficacy and reduce the side effects of THC.

Like other pharmaceutical products, Sativex® is being tested in both preclinical/nonclinical toxicology and safety studies, as well as double-blind, randomized, placebo-controlled clinical trials. Approximately 2,000 patients have gone through such clinical trials, which have examined safety and efficacy in conditions ranging from symptoms of multiple sclerosis (spasticity, bladder dysfunction, tremor, spasm, and sleep disturbance), to central and peripheral neuropathic pain (spinal cord injury, diabetic neuropathy, MS, and brachial plexus avulsion), rheumatoid arthritis, and cancer pain. No adverse drug/drug interaction with opioids has been identified in these patients, many of whom are taking a variety of strong analgesics. Furthermore, in long-term extension studies, patients were able to maintain their symptom relief without having to escalate their dose, indicating that they did not develop tolerance to the therapeutic effects. Sativex® has been tested as an adjunctive treatment exclusively in patients who have had **chronic, intractable symptoms**. Therefore, the symptom relief that these patients experienced was **over and above that achievable with their existing medication regimens**.

In April 2005, Health Canada approved Sativex® for the treatment of neuropathic pain in MS, and the product is being marketed in Canada by Bayer HealthCare. Sativex® is also available by prescription in the U.K. and Spain through government-approved compassionate-access programs. In the U.S., the FDA has allowed Sativex® to enter into late stage (Phase III pivotal) clinical trials in advanced cancer patients whose pain is not adequately controlled by opioids. These trials are expected to begin in early 2007, with an NDA to be submitted approximately 24 to 36 months later.

Conclusion

Cannabinoid research is exploding. In the near future, we can expect that rapid progress will be made in 1) understanding and manipulating the endocannabinoid receptor system, 2) developing new phyto- and synthetic cannabinoid products, and 3) identifying new cannabinoid delivery systems. As our scientific knowledge increases and technology continues to advance, it is likely that regulatory bodies around the world will rightly insist that cannabis-based medicines be developed in accordance with the standards of modern medicine. A new era of medication development, in fact, appears to be just around the corner.

References are available online in the Winter 2006 Bulletin or you may call the CSA office at (800) 345-3691 to request a copy with references.