

Current Status and Future of Cannabis Research

PEER REVIEWED | Ethan B. Russo, MD
Alice P. Mead, JD, LLM | Dustin Sulak, DO

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Although cannabis is primarily viewed by the public as a recreational drug or agent of abuse, its medical application spans recorded history.^{1,2} Evolution has yielded a cannabis plant that produces a family of some 100 chemicals called phytocannabinoids (“plant cannabinoids”), many of which have distinct and valuable therapeutic effects.^{3,4}

Cannabis is a versatile herb that can produce a variety of medicinal preparations with distinct pharmacologic properties, depending on the content of cannabinoids and other phytochemicals, many of which possess synergistic effects.⁴ The best known plant cannabinoid is tetrahydrocannabinol (THC), the primary psychoactive agent in cannabis, responsible for the preponderance of the cannabis “high”; however, it is also a powerful analgesic,⁵ muscle relaxant,⁶ and anti-nausea agent,⁷ among myriad other effects. Coming to greater recognition is its analogue sister, cannabidiol (CBD), which distinguishes itself by its lack of intoxication and its ability to complement the pain relief, antiemetic, anticonvulsant,⁸ and other benefits of THC, while modulating and attenuating its associated side effects (anxiety, tachycardia, et al.).^{4,9-13}



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To gain regulatory approval of a cannabis-based product, pursuing the dietary supplement/botanical path—as opposed to the pharmaceutical one—may be an option for certain preparations. Dietary supplements rarely contain substances with abuse potential, and manufacturers and vendors of such products can make only “structure and function” claims (e.g., “promotes heart health”), rather than medical claims. Therefore, it is probably unlikely that cannabis preparations with a notable amount of THC could be treated as dietary supplements. However, nonpsychoactive cannabinoids, such as CBD could be descheduled (i.e., removed from the federal Controlled Substances Act [CSA]) and developed and marketed as botanical supplements.

Cannabis exerts its effects through a variety of receptor and nonreceptor mechanisms. All vertebrates tested to date harbor an endogenous cannabinoid system (ECS),¹⁴ a regulator of physiological homeostasis whose function has been summarized as “relax, eat, sleep, forget, and protect.”¹⁵ The ECS has three components: endocannabinoids, biosynthetic and catabolic enzymes, and two cannabinoid receptors—CB1, the “psychoactive” neuromodulator that is the most abundant G-protein coupled receptor in the brain, and CB2, a nonpsychoactive immunomodulatory and anti-inflammatory receptor most abundant in the periphery.^{14,16}

Although various surveys support the idea that the American public already accepts the medical utility of cannabis and is acting upon that belief in ever higher numbers, the U.S. Food and Drug Administration (FDA) requires more rigorous proof. Additionally, a survey of Colorado family physicians found that; “Despite a high prevalence of use in Colorado, most family physicians are not convinced of marijuana’s health benefits and believe its use carries risks. Nearly all agreed on the need for further medical education about medical marijuana.”¹⁷

If cannabis-based medicines are to overcome prejudice and gain greater trust from physicians, their production must be standardized and their contents proven safe and efficacious in randomized clinical trials (RCTs) that follow accepted scientific method and are the *sine qua non* of regulatory bodies such as the FDA¹⁸ However, botanical cannabis is highly inconsistent and variable in its chemical composition.

Procedures for standardization of plant-based medicines have been formally presented in the U.S., providing an FDA blueprint for their regulatory approval in the “Guidance for Industry:

Botanical Drug Products.”¹⁹ Meanwhile, although cannabis smoking may not be epidemiologically linked to lung cancer,²⁰ it is responsible for chronic cough, sputum, and cytological changes,^{21,22} which render smoked cannabis an impossible candidate for approval as a prescription product in most jurisdictions.

Anecdotal claims for efficacy of crude cannabis hold no sway for the FDA.¹⁸ There is a relative paucity of published RCT data for inhaled cannabis: the existing trials for pain total only three patient-years of data, whereas the corresponding figure for nabiximols (Sativex®, GW Pharmaceuticals), a standardized oromucosal extract spray combining THC, CBD, and other cannabis components, exceeds 6,000 patient-years of data in published studies of pain, or a two thousand-fold difference.⁵ The latter is also approved in 26 countries for treatment of spasticity in multiple sclerosis, and is currently completing clinical trials for opioid-resistant cancer pain in the U.S. and elsewhere.²³⁻²⁵ This agent has fulfilled criteria of safety and consistency, and has not been abused or diverted to any degree in more than 30,000 patient-years of recorded usage.

Regulatory Challenges and Solutions

The FDA has responsibility for assessing human research and evaluating data from clinical studies. Such research is initiated by an individual researcher in an investigator-initiated trial (IIT) or by a pharmaceutical company. In both situations, an Investigational New Drug (IND) application containing one or more protocols must be presented to, and allowed by, the FDA.²⁶

For industry-sponsored programs, the FDA requires a range of nonclinical/preclinical studies and then clinical trials to demonstrate that the product meets the FDA’s exacting standards of quality, safety, and efficacy in a particular patient population.

The FDA has clarified that it will allow both IITs and RCT development programs with cannabis or cannabis-derived products. Examples of such IITs have been completed and published.^{27,28} An industry-sponsored development program is also progressing with a cannabis-derived product.²⁹ Finally, FDA has promulgated “expanded access” regulations in the *Code of Federal Regulations* in 21 CFR sections 312.310, 312.315, and 312.320, allowing seriously ill patients who lack conventional treatment options and clinical trial opportunities to be treated with an investigational product on a compassionate access basis. More than 300 children

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with various types of medication-resistant epilepsies have been allowed by FDA to receive treatment with a cannabis-derived (but purified) CBD product under such expanded access programs.³⁰

Studies involving herbal cannabis must obtain the material from the National Institute on Drug Abuse (NIDA), which is the sole federally lawful source of research-grade cannabis. NIDA has contracted with the University of Mississippi to grow cannabis (of various cannabinoid ratios and potencies) for research.^{31,32}

FDA has approved at least two products based on botanical extracts; however, FDA has not previously approved any raw botanical/herbal material as a prescription medicine. Such material would face regulatory challenges, such as achieving adequate purity, displaying batch-to-batch standardization, and identifying an appropriate method of delivery (i.e., one that would supply a precise and reproducible dose without the production of toxic by-products).

Cannabis, THC, and products containing botanically or synthetically derived cannabinoids found in the cannabis plant are classified under Schedule I of the federal CSA. The CSA contains five schedules corresponding to a substance's abuse potential and medical usefulness.

Schedule I and II substances are subject to strict security, recordkeeping, and other measures. Substances in Schedule I have "no currently accepted medical use in the U.S." and a high potential for abuse. Substances in Schedule II also have a high potential for abuse, but have an "accepted medical use," a phrase given specific meaning by the federal Drug Enforcement Administration (DEA) and upheld by federal courts:

1. The drug's chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.³³

If FDA approves a cannabis-derived product, such approval constitutes "accepted medical use," and that product will then be moved to a less stringent schedule. Although a substance and a product containing that substance are in the same schedule, "differential" scheduling is possible. For example, Marinol, a product comprising synthetic THC in sesame oil, is classified in Schedule III, whereas other forms of THC remain in Schedule I.³⁴ This may serve as precedent if a cannabis-derived product is FDA approved and rescheduled, although cannabis may remain in Schedule I.

Cannabis's (and THC's) Schedule I status means there are additional hurdles to overcome to conduct research in the U.S. As provided in 21 CFR section 1301.13, a physician who holds a DEA registration (license) to prescribe controlled substances in Schedules II–V may conduct research within those schedules as a "coincident activity" to his or her existing registration, with no further approval from the DEA.

However, to conduct research with a Schedule I substance, an investigator must secure a Schedule I research registration from DEA (which is substance- and protocol-specific), and (often) a Schedule I research license from the state-controlled drugs agency. These additional steps can add three to six months to the time required before an investigator can begin the research project.

A specific medical product cannot be prescribed by physicians and dispensed by pharmacists unless the FDA has approved that product (the "compounding pharmacy" exception is very limited). Therefore, even if cannabis were moved to Schedule II, physicians could not automatically prescribe it directly to patients. Although the NIDA single-source supply is the only domestic source, cannabis-derived products may be manufactured in Europe or elsewhere, and the finished product may be imported into the U.S. for research or ultimately for commercial distribution following FDA approval.³⁵

Current Status of Clinical Cannabinoid Medicine

Due to the obstacles involved in human clinical research using cannabis, widespread use in the clinical setting has preceded well-established data on dosage, delivery systems, safety, and efficacy. In states that have legalized medical cannabis, about 0.77% of the population use cannabis with the recommendation of a medical provider.³⁶

Although various surveys support the idea that the American public already accepts the medical utility of cannabis and is acting upon that belief in ever higher numbers, the U.S. Food and Drug Administration (FDA) requires more rigorous proof.

Cannabinoids are considered nonlethal and have a wide range of effective and tolerated dosages. Many patients use medical cannabis in a harm-reduction paradigm to decrease or discontinue the use of prescribed and illicit substances.³⁷ Also, the growing number of medical providers accepting cannabis as a viable treatment option³⁸ may attest to observed or suspected clinical efficacy. Meanwhile, observational studies can inform the emerging clinical practice of cannabinoid medicine, while guiding the development of clinical experimental design.³⁹

One of this article's authors has observed clinical responses in his patient population in oral doses beginning as low as 0.1 mg cannabinoids/kg body weight/day, whereas some find optimal benefits at doses as high as 25 mg/kg/day. This wide dosing range is complicated by a biphasic dose-response curve, where lower doses may exhibit greater efficacy and tolerability than higher doses, as seen in a clinical trial of nabiximols for poorly controlled chronic pain in opioid-treated cancer patients.²⁴

Another clinical trial of inhaled cannabis for neuropathic pain found low-potency (3.5% THC) and high-potency (7% THC) cannabis to have equivalent analgesic properties.²⁷ Biphasic dose-response effects may be due to subjects' sensitization to cannabinoids at lower doses and tolerance building at higher doses. This hypothesis is supported by preclinical studies in which administration of exogenous cannabinoids both upregulate endocannabinoid system function at acute and lower doses via increased endocannabinoid production,⁴⁰ cannabinoid receptor expression,⁴¹ and cannabinoid receptor affinity,⁴² and downregulate endocannabinoid system function upon persistent agonism via membrane receptor endosome internalization.⁴³

Bidirectional effects are often related to dosage,^{44,45} with high doses of cannabinoids potentially causing symptoms usually ameliorated by lower dosages. The mindset of the cannabis user and setting in which the cannabis use takes place also influence bidirectional effects; anxious subjects tend to become less anxious and more euphoric, nonanxious individuals tend to become somewhat more anxious,⁴⁶ and stressful environments can precipitate adverse emotional responses.⁴⁷

Polymorphisms have been associated with variable responses to cannabis, including protective effects on development of cannabis dependence in adolescents,⁴⁸ intensity of withdrawal and craving during cannabis abstinence,⁴⁹ and white matter

volume deficits and cognitive impairments in schizophrenic heavy cannabis users.⁵⁰

Cannabis use history also complicates clinical response, with cannabis-naïve patients demonstrating more frequent adverse effects⁵¹ and regular users demonstrating less psychotomimetic, perceptual altering, amnesic, and endocrine effects.⁵²

Another factor to note is that physicians often lack training in using botanical medicines, and endocannabinoid physiology is still absent from most medical school curricula. Many legal cannabis patients receive permission to use cannabis from their physician, but must rely on formula selection and dosing instructions provided by cannabis growers or dispensary staff with little training or experience.

Properly interpreting observational data on medical cannabis patients requires an understanding of the chemical composition and potency of the cannabis preparations used, and of the pharmacokinetics of the delivery system employed. Laboratories offering third-party chemical analysis of herbal cannabis preparations under industry-published standards⁵³ can be found in most states that allow the use of medical cannabis.⁵⁴

Conclusion

The endocannabinoid system regulates physiologic homeostasis and is an exciting target for disease management and health promotion. Cannabis-based preparations are poised to become an accepted option in mainstream medicine, with broad support from preclinical models, patient testimonials, and more recently, human clinical trials.

However, numerous regulatory, botanical, and pharmacologic factors challenge the collection and interpretation of clinical data on the efficacy of cannabinoid therapies. The understanding of an individual's optimal dosing and delivery method of cannabinoids for various ailments is still emerging, and must be guided by both observational and experimental data.

Clinical researchers can overcome the challenges inherent in cannabinoid therapeutics and help elucidate solutions for a wide variety of prevalent health challenges.

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Ethan B. Russo, MD, (erusso@phytecs.com) is medical director of PHYTECS and past president of the International Cannabinoid Research Society.

Alice P. Mead, JD, LL.M., is vice president, U.S. Professional Relations, GW Pharmaceuticals.

Dustin Sulak, DO, (drsulak@gmail.com) is founder and medical director of Integr8 Health, Falmouth, Maine.

Clear the Mud: Current and Future of Cannabis Research.

The authors of this article will be joined by Sean McAllister, PhD, to speak at a two-hour session presented during the ACRP Global Conference in Salt Lake City on Sunday, April 26 from 8:30 AM to 10:30 AM. Learn firsthand where they see this new and “exploding” industry going. They will discuss the current and future of cannabis research from the perspective of a pharmaceutical physician, regulatory and legal expert, basic researcher, and practicing physician.

