Medical Cannabis: Bridging Science and Policy

Margaret Haney, PhD, speaks to conference attendees at Columbia University in New York City.

New York, NY—Vast changes in cannabis public policy have occurred over the past 20 years with little scientific input, Margaret Haney, PhD, told attendees at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University.[1]

"Putting medical cannabis decisions up to vote has led to this crazy patchwork across our country where in New Jersey you can use cannabis for migraines, but in New York you cannot. The decision is not based on science. It is based on who was lobbying in that particular state," said Dr. Haney, who is Director of the Cannabis Research Laboratory and Co-director of the Substance Use Research Center at NewYork-Presbyterian/Columbia University Irving Medical Center, and Professor of Neurobiology (in Psychiatry), at Columbia University in New York City. "While legalization of recreational use is perfectly within the purview of voters in a democracy, it is deeply troubling to have voters vote on what constitutes an efficacious medication," she added.

Although Dr. Haney noted that medical cannabis has shown "tremendous potential" in the treatment of a variety of conditions, including pain, obsessive compulsive disorder (OCD), and food intake in patients with HIV,[2] the current understanding of the therapeutic use of cannabis and cannabinoids is still in the early stage. "Cannabis has escaped the process required of every other prescribed medication, and that is randomized placebo-controlled evidence," Dr. Haney told meeting attendees.

Legal Barriers to Cannabis Research

Although randomized controlled trials using safely manufactured products of known composition are the key to closing the gap between science and policy, trials are difficult to conduct as statewide legalized recreational or medical cannabis legislation does not extend to scientific study. Dr. Haney emphasized the need to reclassify cannabis and its constituents to a Schedule II status to open the pathway for scientists to conduct more placebo-controlled trials.

Presently, cannabis and its constituents remain Schedule I substances according to the Drug Enforcement Administration (DEA) with the exception of Epidiolex (cannabidiol [CBD]), which is approved for the treatment of Lennox-Gastaut syndrome or Dravet syndrome.[3] "Currently, there is no US source of FDA-approved CBD for scientific research, so how can we test this drug?" Dr. Haney asked attendees.

Dr. Haney discussed the following regulatory hurdles:

- For scientists who would like to conduct federally funded clinical research, the DEA has only approved one source of cannabis from a farm at the University of Mississippi
- Each investigator needs federal/local DEA and state licenses as well as FDA approval (investigational new drug application) for each protocol
- Cannabinoids—including oral CBD—must be stored in a gun safe in a double-locked and alarmed room, and each Schedule I-licensed investigator needs a separate safe
- Cannabinoids/cannabis can only be administered on site, limiting research for chronic conditions that require ongoing use and longitudinal analysis

An additional issue is that cannabis "has morphed into this large-scale, for-profit industry and, in lieu of evidence, the medical benefit is really what the marketers are saying it is because the FDA has stayed remarkably silent for the most part on all of this," Dr. Haney said.

Cannabis Research Laboratory

At the Cannabis Research Laboratory at Columbia University, Dr. Haney collaborates with researchers from many different specialties including oncology, pain medicine, and psychiatry. Currently, she is enrolling patients in the laboratory's first randomized placebo-controlled trial using FDA-approved CBD:delta-9-tetrahydrocannabinol (THC) capsules imported from Canada.

"This is a well-powered, placebo-controlled trial," Dr. Haney said. "We have patients underway and are conducting biweekly measures of pain and functional impairment."

The researchers are evaluating the effects of cannabis capsules containing high CBD:low THC (n=48) compared with placebo (n=48) given for 8 weeks in women with taxane-induced peripheral neuropathy (TIPN). This side effect occurs in more than 65% of patients treated for breast cancer, and no effective treatment is currently available. As a result, TIPN causes a significant number of women to terminate chemotherapy. In animal models, CBD and THC given before paclitaxel prevented development of TIPN, and significantly reduced symptoms when given after onset of TIPN.[4,5] A proposed mechanism behind this effect is agonism at the serotonin 1A receptor.[5]

The laboratory provides a unique setting for clinical trials as it contains 4 bedrooms in addition to a recreational space, and allows for around-the-clock monitoring of mood and drug effects, sleep, cognitive performance, and other measures. "I bring in 4 people to live in the lab at a time, and I have them smoke controlled amounts of cannabis throughout the day and then placebo cannabis as well," said Dr. Haney.

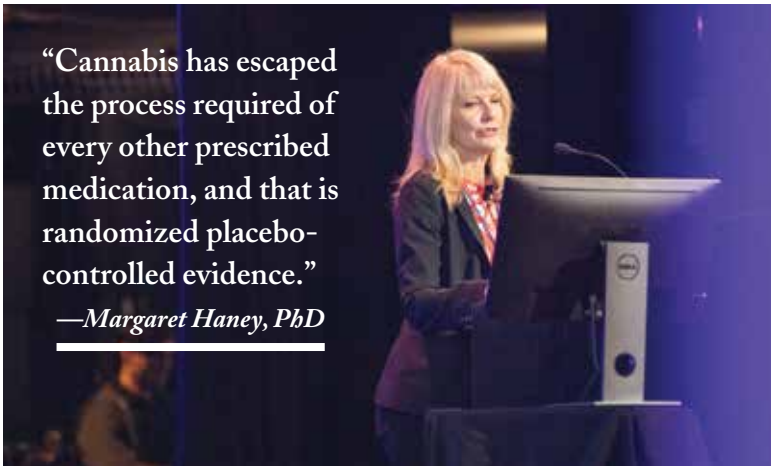
In a study at the laboratory using a cold presser task experimental pain model, researchers examined the analgesic effects of dronabinol versus cannabis among daily cannabis smokers. Study findings revealed that cannabis and dronabinol produced a comparable magnitude of analgesia compared with placebo in healthy male (n=15) and female (n=15) cannabis smokers.[6] However, dronabinol showed longer-lasting effects and only cannabis produced abuse-related effects, Dr. Haney noted.

In a more recent study of experimental pain in healthy cannabis smokers (N=18), neither cannabis nor a subtherapeutic dose of oxycodone (2.5 mg) produced an analgesic effect; however, when these agents were combined, a significant synergistic effect on pain threshold and tolerance was found ($P \leq 0.05$).[7]

"This suggests that a subtherapeutic dose of oxycodone paired with active cannabis could give a nice analgesic effect, supporting

the notion that you could tentatively use less opioids and get a significant analgesic effect," Dr. Haney said. This synergistic effect was not found with higher doses of oxycodone.[7]

However, the analgesic effect of cannabis may only be found in men, according to research by Dr. Haney and Ziva D. Cooper, PhD, Research Director of the UCLA Cannabis Research Initiative in the Jane and Terry Semel Institute for Neuroscience and Human Behavior, and the Department of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles.[8] In a study involving 21 male and 21 female cannabis smokers, an experimental model of pain showed that active cannabis significantly decreased pain sensitivity compared with inactive cannabis in men ($P<0.01$) but not in women. Men and women in this study were matched for current cannabis use, to rule out the potential effects of tolerance to cannabis.



"Women tended to be more sensitive to the abuse potential of cannabis, but less sensitive to the analgesic effect," Dr. Haney told the *American Journal of Endocannabinoid Medicine*.[8] The mechanism behind this difference is unclear, she said.

Future Research

Dr. Haney emphasized the need for future placebo-controlled trials of cannabis in the treatment of glioblastoma and post-traumatic stress disorder (PTSD). Additionally, Dr. Haney said that more research on the effects of the bioavailability of different routes of cannabis administration, dose, and sex on outcomes is urgently needed.

"We've shown in our small studies, evidence for efficacy of cannabis in pain, OCD, and food intake in patients with HIV, but our understanding of the therapeutic use of cannabis and cannabinoids is still in its infancy," Dr. Haney said.[9] "We have to consider the potential placebo effects of cannabis because the majority of data in the field is observational."

Current Knowledge on Cannabis Efficacy

Finally, Dr. Haney outlined current evidence-based research findings to meeting attendees. She cited a 2017 report from the National Academies of Science, Engineering, and Medicine showing conclusive or substantial evidence that cannabis or cannabinoids are effective for the following[2]:

- Treatment of chemotherapy-induced nausea and vomiting
- Improving patient-reported spasticity in multiple sclerosis
- Treatment of chronic pain in adults

A randomized placebo-controlled trial demonstrated efficacy of CBD as an adjunct to antiepileptic drugs in the treatment of drug-resistant seizures in children with Dravet syndrome, with a reduction in the median frequency of convulsive seizures from 12.4 to 5.9 per month.[10] A reduction in convulsive-seizure frequency of at least 50% was found in 43% of patients who received CBD compared with 27% of patients in the placebo group ($P=0.08$).

Dr. Haney said there was insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders, pointing to a 2019 meta-analysis of cannabis use in psychiatric disorders.[11] The study found "scarce evidence" that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit/hyperactivity disorder, Tourette syndrome, PTSD, or psychosis. Additionally, there was "very low-quality evidence" that THC use (with or without CBD) leads to a small improvement in symptoms of anxiety in patients with other medical conditions.

References

1. Haney M. Medical cannabis: published evidence, current research. Presented at: Medical Cannabis: The Science. The Research. The Risks.; November 15, 2019; New York, NY. Accessed February 23, 2020. www.medicalcannabis-science-research-risks.com
2. National Academies of Sciences, Engineering, and Medicine 2017. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.
3. Epidiolex (cannabinol) [package insert]. Carlsbad, CA. Greenwhich Biosciences Inc.; Revised December 2018.
4. Ward SJ, Ramirez MD, Neelakantan H, Walker EA. Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female C57Bl6 mice. *Anesth Analg*. 2011; 113(4):947-950.
5. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. *Br J Pharmacol*. 2014; 171(3):636-645
6. Cooper ZD, Comer SD, Haney M. Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. *Neuropsychopharmacology*. 2013;38(10):1984-1992.
7. Cooper ZD, Bedi G, Ramesh D, Balter R, Comer SD, Haney M. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. *Neuropsychopharmacology*. 2018; 43(10):2046-2055.
8. Cooper ZD, Haney M. Sex-dependent effects of cannabis-induced analgesia. *Drug Alcohol Depend.* 2016;167:112-120.
9. Haney M, Gunderson EW, Rabkin J, et al. Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr*. 2007;45(5):545-554.
10. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376(21):2011-2020.
11. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6(12):995-1010.

Dr. Haney *has no financial conflicts of interest to disclose.*