The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JULY 25, 2019

# The Opportunity of CBD — Reforming the Law

Pieter A. Cohen, M.D., and Joshua Sharfstein, M.D.

Over the past year, dietary supplements and foods containing cannabidiol (CBD) have swept into retail establishments and onto the Internet, with estimated annual U.S. sales now exceeding $200 million and growing rapidly. Recently, however, the Food and Drug Administration (FDA) has taken the position that CBD cannot be legally sold in either supplements or foods.[1] As many manufacturers defy the FDA's position, this moment may provide an unexpected opportunity to improve the oversight of supplement ingredients and additives to food.

CBD is one of more than 80 active compounds in recreational cannabis, but it does not have the potent psychoactive effects of its chemical cousin delta-9-tetrahydrocannabinol (THC).[1] It does have a reputation among cannabis enthusiasts for a broad range of healing properties. However, CBD's only FDA-approved indication as a medication is to treat intractable seizures in patients with the Lennox–Gastaut syndrome or the Dravet syndrome. No large high-quality clinical trials examining other benefits have been conducted.

The FDA has raised concerns regarding the long-term safety of CBD. In clinical trials, adverse effects have included diarrhea, somnolence, decreased appetite, and increased levels of liver enzymes.[2] In light of these and other safety concerns, including pregnancy-related risks, the FDA has required multiple postmarketing safety studies.

One factor driving the nonpharmaceutical use of CBD is a ready source of the chemical. CBD can be isolated from both recreational cannabis and hemp, a variant of the cannabis plant cultivated for fiber and other industrial uses. The 2018 Farm Bill removed hemp (with THC levels below 0.3%) from the list of controlled substances. U.S. farmers have begun to replace some corn, soybeans, and even tobacco with cannabis with low levels of THC, with the intention of supporting the production of an ever-expanding array of CBD products.

Indeed, many store shelves now feature CBD oils, gummy candies, joint balms, capsules, and other products. In December 2018, however, the FDA cast a shadow over the industry by stating that CBD may not be sold in food or supplements on the grounds that the chemical has already been approved as a drug. The agency further explained that were this obstacle (which is based in federal statute) to be overcome, CBD would then be subject to oversight either as a "new dietary ingredient" in supplements or as a food additive.[1]

In response, some states began taking products containing CBD

off the market. In other areas, however, manufacturers and local officials are disregarding federal law, much as some states permit the sale of recreational cannabis. The FDA, for the time being, has focused its limited enforcement resources on removing CBD products that make claims of curing or treating disease, leaving many CBD products available for sale.

We thus seem to be headed toward a confusing, uneven, and potentially risky market in CBD products. This situation creates an opportunity for Congress to take action.

One approach could be for legislation to simply deem CBD legal at certain doses for use in dietary supplements and foods. It would be impractical and inappropriate, however, for Congress itself to make determinations about the safety of CBD or other individual chemicals. These decisions should be made by the FDA, the scientific agency whose job it is to protect the public from unacceptable risks.

A more responsible approach would be for Congress to pass a law that both waives the prohibition created by CBD's prior approval as a drug and creates clear, reasonable pathways for low-dose CBD and other new substances to be safely introduced into supplements and food.

The Dietary Supplement Health and Education Act of 1994 created the regulatory framework under which the FDA today oversees vitamins, minerals, botanicals, live microorganisms, and other products marketed as dietary supplements — a market worth $40 billion in sales per year.[3] The law requires manufacturers that plan to market a new ingredient as a dietary supplement to submit a premarket notification to the FDA. The manufacturer is expected to share information with the FDA that the ingredient "will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling." If the agency acknowledges the application without posing additional concerns or questions, the new ingredient may be introduced into commerce.

In practice, however, this process is broken. The law does not require that firms submit studies conducted in humans, and firms may use weak evidence, such as historical use in foreign countries, to support conclusions about an ingredient's safety. In addition, some companies attempt to cite the natural presence of trace amounts in food to claim that ingredients can bypass the premarket notification altogether. Others simply sell products with questionable ingredients without informing the FDA. Furthermore, the FDA lacks an effective system for tracking which of the estimated 80,000 supplement products on the market contain one or more new ingredients.

These gaps have allowed companies to market products with highly concentrated chemicals that have caused serious adverse effects. For example, in 2013, epidemiologists traced a national outbreak of hepatitis leading to dozens of hospitalizations, three liver transplantations, and two deaths to a mixture of highly concentrated synthetic ingredients sold as a dietary supplement.[4]

A new CBD law could require the FDA to strengthen its approach to safety requirements for new dietary ingredients, prohibit the risky practice of concentrating ingredients in supplements at levels much higher than those traditionally found in food or botanicals, and create an effective mandatory product listing for all dietary supplements. A listing requirement is especially important in cases of newly introduced substances, such as CBD, for which safety issues may not be fully understood until there is broader public exposure.

To add a substance to food, manufacturers today can convene experts to determine whether the proposed additive is "generally recognized as safe" (GRAS) under the "terms of its intended use." Manufacturers next have the option, but are not required, to inform the FDA that they have determined that a substance is GRAS.[5]

This pathway also has weaknesses. Companies have convened their own experts, determined that a substance is GRAS under the terms of its intended use, and incorporated the substance into food before the FDA was even aware of what was happening.

A CBD law could ensure that, moving forward, the GRAS determination would be made only by independent experts and that manufacturers would inform the FDA of all GRAS determinations before marketing.

What's possible, then, is a deal. Congress could remove one major barrier to marketing low doses of CBD in dietary supplements and foods, while closing long-standing gaps in oversight of these products.

As with any compromise, objections might arise from all sides. Supplement firms that do not sell CBD might object to more rigorous requirements for other new ingredients, and physicians might express concern over whether manufacturers would have an adequate incentive to perform high-quality clinical studies for new indications. A well-crafted bill,

however, would increase consumer confidence in supplements in general, helping all legitimate companies, and would preserve incentives for research into highly concentrated CBD and other chemicals with botanical origins.

While not perfect, such a compromise would have something to offer farmers, manufacturers, consumers, cannabis enthusiasts, and health care professionals. Whatever its health benefits turn out to be, CBD could well prove to have beneficial effects for the safety of all supplements and foods in the United States.

*An audio interview with Dr. Cohen is available at NEJM.org*

Disclosure forms provided by the authors are available at NEJM.org.

From Harvard Medical School, Boston (P.A.C.); and the Johns Hopkins Bloomberg School of Public Health, Baltimore (J.S.).

This article was published on June 12, 2019, at NEJM.org.

1. Food and Drug Administration. FDA regulation of cannabis and cannabis-derived products: questions and answers. 2019 (https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers).
2. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. N Engl J Med 2018;378:1888-97.
3. Dietary Supplement Health and Education Act of 1994. Pub. L. No. 103-417, 1994. 103rd Congress, 2nd sess., S784.
4. Chatham-Stephens K, Taylor E, Chang A, et al. Hepatotoxicity associated with weight loss or sports dietary supplements, including OxyELITE Pro — United States, 2013. Drug Test Anal 2017;9:68-74.
5. Neltner TG, Alger HM, O'Reilly JT, Krimsky S, Bero LA, Maffini MV. Conflicts of interest in approvals of additives to food determined to be generally recognized as safe: out of balance. JAMA Intern Med 2013;173:2032-6.

DOI: 10.1056/NEJMp1906409


# Implications of an Aging Rural Physician Workforce

Lucy Skinner, B.A., Douglas O. Staiger, Ph.D., David I. Auerbach, Ph.D., and Peter I. Buerhaus, Ph.D., R.N.

Rural areas in the United States suffer disproportionately from inadequate access to health care. In 2018, according to the Health Resources and Services Administration (HRSA), 66% of Health Professional Shortage Areas for primary care and 62% of those for mental health were located in rural or partially rural areas of the country. Although there is disagreement about the adequacy of the overall physician supply, there is little disagreement that the uneven distribution of physicians presents serious access problems in many rural areas. Limited access to physicians can reduce access to preventive care and exacerbate unmet health needs, leading to costly hospitalizations and poor health status.

Despite concerns about the number of physicians practicing in rural areas who are nearing retirement age, very little is known about the implications of an aging rural physician workforce for future physician supply in these areas. Maintaining physician supply in rural areas has important equity implications, given that, as compared with more urban populations, rural residents are likely to be older and poorer, are more commonly uninsured, and have lower life expectancy.

We used data on physician age and location from the U.S. Census to establish recent trends in the age distribution of rural physicians and used this information to forecast workforce growth through 2030. Our primary data originate from the American Community Survey (ACS) Public Use Microdata Sample (PUMS) conducted by the U.S. Bureau of the Census, which collects information on respondents' occupation, hours worked, age, and location of residence.[1] We used data on all physicians 28 to 74 years of age from the 2005 to 2017 ACS surveys and similar information from the 2000 Census 5% sample (n=153,822) and converted these counts to full-time equivalents (FTEs).

We used the HRSA approach to identify rural residence,[2] assigning physicians rural status (n=14,076) if their household was in a Public Use Microdata Area (PUMA) in which the majority of the population lives in a nonmetropolitan area. U.S. population size was calculated using Census data stratified into rural and urban areas, and estimates of the rural population after 2017 were based on a United Nations growth forecast. We projected the number of physicians through 2030 using our forecast model (described by Buerhaus et al.[3]), which takes into account life-cycle workforce-participation patterns associated with age (age effects) and differences among birth cohorts in entry into the profession (cohort effects).

From 2000 to 2017, the age distribution of rural physicians shift-