Enhancing Methodological Approaches for Studying Health Effects of High-Concentration THC Products

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For public health protection, informed decision-making relies on having a robust foundation of evidence concerning risks and their prevention. Application of an evidence-based framework depends on the availability of pertinent, scientifically sound data generated by well-directed and valid research endeavors.

In this essay, we address the current state of research in humans and the evidential base concerning high-concentration delta-9-tetrahydrocannabinol (delta-9-THC) products, which are readily available in the United States. Furthermore, we explore the intricate challenges faced in carrying out research on these products, which reflect the full range of study design issues: measurement of exposure and outcomes, confounding, selection bias, and the generalizability of findings.

We offer recommendations to guide future research toward providing more informative evidence. By following these recommendations, researchers and funders on this emerging topic could move toward generating the valid and comprehensive evidence needed to effectively inform public health initiatives and guide policy decisions regarding high-concentration delta-9-THC products and their use. The urgency of generating such evidence cannot be overstated, given the widespread legalization and increasing availability and use of these products. (*Am J Public Health*. 2024;114(S8):S639–S644. https://doi.org/10.2105/AJPH.2024.307724)

In the past few decades, the United States has experienced a profound transformation in its approach to cannabis regulations with implications for access and for the products used. Historically, cannabis was largely prohibited across the nation, and it has long been listed as a Schedule I drug under the Controlled Substances Act.[1] However, this landscape began to change in the late 20th century, when California became the first state to legalize medical cannabis in 1996. In 2012, Colorado and Washington were the first states to approve legal recreational use (or more recently termed "adult use"). As of November 2023, 38 states, 4 US territories, and the District of Columbia allowed medical cannabis, and 24 states, 3 US territories, and the District of Columbia had legalized adult-use cannabis.[2]

This evolving regulatory framework has given rise to a dynamic cannabis market, characterized by diverse products, consumption methods, and increased delta-9-tetrahydrocannabinol (THC) concentration in cannabis products. During the period spanning the 1960s through the 1980s, the typical THC concentration in cannabis flower ranged from 2% to 4%. Presently, cannabis flower in the United States has an average THC concentration of 20%.[3] Within today's market, THC-containing inhalational products (e.g., vaping) are capable of delivering THC at concentrations as high as 70% to 90%.[4] The rising access to cannabis products with far higher THC concentrations than previously available has raised concern regarding the associated risks,

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particularly to adolescents and young adults who use these products at an age when they may be particularly susceptible to poor outcomes both presently and in the future.

THE GLOBAL PICTURE OF THE CANNABIS MARKET

While the United States is the largest market for adult-use cannabis, it is legal in other countries including Uruguay, Thailand, Spain, Canada, and South Africa.[4] Medical use is legal in many countries as well. As in the United States, the THC concentration has been rising over time in cannabis flower seized in Europe.[5,6] The Canadian cannabis market offers high-concentration products and novel modes of using high-concentration products.[7] Unlike the United States, Canada has legalized cannabis nationwide (rather than state by state), although provinces and territories are allowed to set their own regulations and restrictions. In 2022, the Canadian Cannabis Survey (n = 10 048) reported that of those who used cannabis in the previous 12 months, smoking it was most common at 70%, but 52% consumed cannabis in an edible product, 41% used an inhaled product (vape pen, e-cigarette, or vaporizer), and 6% dabbed cannabis.[8] Uruguay has had limits for THC concentration in cannabis products since sales began in 2017, increasing from 2% to 9% THC[9] and then to 15% in December of 2020.[10] However, use of high-concentration products is not limited to countries that have legalized cannabis. In Europe, despite the illegal status, the 2021 European Web Survey on Drugs (n = 51 304) found that respondents who used cannabis in the past 12 months used alternative or high-concentration cannabis products including resins (32%), edibles (25%), and extracts (17%).[11] Research findings on high-concentration THC products have global relevance.

EVIDENCE BASE FOR HIGH-CONCENTRATION THC PRODUCTS

The Colorado General Assembly, concerned by the availability of high-concentration THC products in the state's cannabis marketplace, passed House Bill 21-1317 (HB 1317) in 2021.[12] Among its provisions, HB 1317 called on the Colorado School of Public Health to "conduct a systematic review of all available scientific evidence-based research regarding the possible physical and mental health effects of high-potency THC marijuana and marijuana concentrates regardless of the location of the research."[12] With this direction, we completed a scoping review, identifying 452 studies that met the criteria for relevance to the critical policy question: What are the public health consequences of the availability of these newer products with higher concentrations of THC than were previously available?[13] In this scoping review, we included human studies of any epidemiological design, without restrictions based on age, sex, health status, country, or outcome measured, as long as they reported delta-9-THC concentrations or included a known high-concentration THC product. The literature covered in the scoping review is a mix of clinical trials directed at therapeutic uses and observational studies, primarily addressing potential adverse consequences. Here, we focus on the latter body of evidence, which is more relevant to the policy question we posed. Overall, we found the evidence foundation profoundly lacking for addressing this critical question and supporting informed decision-making.

Most critically, the research was limited by highly variable and incomplete approaches to measuring cannabis use and THC exposure. The THC exposure dose, or amount of THC entering the body, depends not only on product concentration but also on route of administration, frequency of use, duration of use, self-titration, and characteristics of the individual using the product such as age and comorbidities. An individual's tolerance affects the exposure dose to achieve the desired effect. However, collecting data on these aspects of consumption history, exposure dose, and response poses a complex challenge. Study participants often consume a variety of products with diverse usage patterns and have varying tolerance levels. Our scoping review revealed a wide range of approaches to assessing exposure to cannabis products, with most studies relying on self-report and falling short in capturing the comprehensive array of elements required to estimate exposure dose accurately.[13] Moreover, many studies understandably failed to address the concentrations of various cannabinoids (e.g., product used). The absence of information on this chemical profile potentially complicates the interpretation of results and may become an increasing source of uncertainty as the diversity of cannabinoid-containing products in the marketplace increases. These challenges in the measurement and reporting of exposure-related factors hinder the evaluation of the association between exposure and the likelihood of adverse or beneficial health outcomes. Using an incomplete consumption history to estimate risks for effects comes with the potential for bias, both nondifferential and differential, which

might increase or decrease estimates from the true value and inherently increases uncertainty.

The evidence in the scoping review was further weakened by selection bias, unmeasured and uncontrolled confounding, substantial heterogeneity in how study outcomes were measured, and the limited generalizability of many studies for products used today. To illustrate the last point, a 2018 survey of the THC concentration in herbal cannabis products across 7 states permitting cannabis use revealed that, in most products in these states, THC concentrations were between 15% and 30%.[14] In some states, such as Maine, more than 70% of products sampled exceeded 15% THC, while in Colorado, this figure exceeded 91%. Notably, cannabis concentrate products have seen a substantial increase in THC concentration, rising from an average of 46% THC in 2014 to 68% THC in 2020.[15] Our scoping review documents a wide range of concentrations in the cannabis products that have been studied, with a median concentration of 12%, significantly below the levels available in today's market.[13]

One possible reason for the observed lower concentration of THC in numerous studies funded by the National Institutes of Health is the restriction on cannabis used for research in the United States. Historically, experimental research has been confined to cannabis supplied exclusively by the National Institute for Drug Abuse Drug Supply Program.[16] However, more diverse products have become accessible for research purposes through recently authorized growers regulated by the Drug Enforcement Administration.[16,17] Despite this progress, the range of cannabis products studied in the literature has remained narrow, featuring lower concentrations than those readily obtainable from local dispensaries or the illegal market.[18]

In addition, ethical concerns arise when attempting to investigate the chronic use and long-term effects of cannabis with experimental designs. Obtaining permission to use cannabis for clinical research remains complex for both the Food and Drug Administration (FDA) and academic institutions. The FDA has provided specific guidance on submitting an Investigational New Drug Application for botanical products such as cannabis.[19] Researchers need to understand these regulations, other issues related to the FDA,[20,21] and institutional requirements to navigate the complex landscape of clinical trial compliance and drug development involved in using cannabis in research.[19]

RECOMMENDATIONS FOR FUTURE STUDIES OF CANNABIS PRODUCTS

Given the urgency of having credible and certain evidence to support policy formulation, deficiencies of research approaches need to be addressed and an overall plan developed to strategically guide research to address critical uncertainties in the evidence foundation. Based on insights from the scoping review, we offer 6 recommendations to enhance research on high-concentration delta-9-THC products. The recommendations speak to the lack of rigor and relevance in research to date, acknowledging the challenges that those investigating cannabis have faced:

1. Future studies should (1) explicitly define the causal effect of interest, including the specification of exposure and dose, and (2) apply validated and standardized tools and instruments to measure exposure and dose per the causal effect of interest. These approaches need to be modified in a timely way so that the data collected for research reflect actual patterns of use.
2. Future studies should employ rigorous experimental and observational designs to reduce the threats to internal validity introduced by confounding, considering the full suite of potential confounders.
3. Researchers should establish clear and well-defined eligibility criteria and provide a comprehensive description of the recruitment process, enabling users of the information to assess the extent of potential selection bias in observational cannabis research. Efforts should be made to minimize attrition and loss to follow-up.
4. Researchers should implement core outcome sets in future cannabis studies. By adopting a core outcome set, researchers can establish a standardized set of outcomes that should be consistently measured and reported across studies.
5. Researchers should consider and leverage advanced causal inference design and analytical approaches to addressing potential biases in observational studies of cannabis use.
6. To enhance the generalizability of cannabis research, researchers should strive to ensure more representative and diverse samples from the target populations. Efforts should be made to encourage participation from underrepresented groups by employing inclusive

recruitment strategies and addressing the stigma associated with cannabis use.

The responsibility for facilitating the development of standardized methods for exposure assessment and the assembly of a strategic research agenda lies at the intersection of various stakeholders and institutions. An independent and transparent research agenda requires collaboration among government agencies, research institutions, public health organizations, the cannabis industry, consumers, and experts in the field of cannabis research. Standardization of exposure dose assessments should include universal and comprehensive questions on patterns of use, biomarkers to quantify exposures, language defining cannabis products and their THC concentrations that translate across cultures, and standardization of THC exposure dose units that can translate between routes of exposure (e.g., ingestion, combustion, vaporization) and THC units of measure (e.g., % THC and mg THC).[22,23]

In addition, this same broad set of players should identify key research priorities and policy-relevant questions to inform evidence-based decision-making. We urge the development of a strategic framework for research on high-concentration THC products. This strategic agenda should prioritize critical areas such as youth consumption patterns, associated behavioral and mental health outcomes, and the consequences of use during pregnancy, and should also include a focus on addressing health equity concerns related to cannabis use.

There are models for such agendas (e.g., the framework proposed by the National Research Council [now known as the National Academy of Sciences, Engineering, and Medicine]) to guide research on airborne particulate matter.[24] This framework aimed to facilitate the understanding of the sources, characteristics, and health effects of airborne particulate matter and was influential in shaping research and policy in this field. Its fundamental components encompassed the thorough characterization of particulate matter, rigorous exposure assessment, in-depth exploration of health effects, comprehensive toxicological investigations, expansive epidemiological studies, meticulous risk assessment, informed policy and regulatory decisions, and effective public communication and education efforts. Remarkably, these core elements of the framework bear relevance to the realm of cannabis research. By fostering a multidisciplinary, coordinated approach, stakeholders can effectively elevate the rigor, comprehensiveness, and responsiveness of research in this domain, aligning it with the pressing policy imperatives concerning high-concentration THC products.

Regarding confounding, it is important to recognize that potential confounders may go unidentified, their measurement may be inaccurate, and the methods or models employed for confounder adjustment may be misspecified. We encourage researchers to consider causal inference strategies in both the design and analysis of observational data, giving attention to the underlying causal structure to the extent that it is understood. Approaches such as trial emulation,[25] propensity scores,[26] instrumental variables,[27] interrupted time series,[28] difference-in-difference,[29] and regression discontinuity,[30] when applied properly, can facilitate causal inference in the absence of randomization. To mitigate the influence of selection bias and enhance generalizability in observational cannabis research, meticulous attention must be given to the selection of a study population that closely represents the target population.

Lastly, it is worth noting that core outcome sets have gained widespread recognition as an integral part of the solution to the current problems with outcomes in studies, including those involving cannabis. A core outcome set represents a consensus-based, minimum set of outcomes (usually 5–7), typically agreed upon by a community of stakeholders, that will be measured and reported in research in a given disease area.[31,32] The existence and utilization of an agreed-upon core outcome set recognize that certain outcomes are important, valid, and relevant to the community's knowledge; facilitate consistency in outcomes across studies; and facilitate incorporation of critical outcomes from all relevant studies in evidence syntheses.

The cannabis industry has undergone a remarkable expansion in recent years. It is already a global industry and likely to grow in more countries. As legalization efforts have gained momentum, the cannabis market has already evolved into a multibillion-dollar industry encompassing a wide array of products. Despite this industry's substantial growth, there is a notable gap in parallel research and timely evidence development. The rapid emergence of new cannabis products, especially those with high concentrations of THC, underscores the urgency for comprehensive research and surveillance data collection. This discrepancy between the industry's burgeoning scope and the lag in evidence generation raises critical questions about the potential public health risks and regulatory approaches, absent the evidence

needed for formulating appropriately protective policies. The lack of evidence also hinders the development of campaigns to inform the public about these products. As the marketplace evolves, the lessons gleaned from experience with delta-9-THC are poised to echo through other novel products and use of non–delta-9-THC cannabinoids (including hemp), underscoring the significance of the insights gained. Addressing this disconnect is imperative to ensure that policy decisions align with the evolving landscape of cannabis production and consumption, ultimately safeguarding public health and well-being. AJPH

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