

Emerging Topics and Innovative Methodologies in Cannabis Research

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AIMS AND SCOPE: Cannabis use is ascendant in our society, affecting the health of our citizens, our social norms and social structures, and our economies. This special issue brings together a diverse set of research manuscripts that push the borders of our understanding of burgeoning cannabis use and displays innovative methods developed to study these phenomena.

Introduction

Over the past 10 years, increasing numbers of US states have passed medical and recreational cannabis laws.¹ More than two-thirds of the adult population in the United States now have legal-access cannabis for medicinal or recreational purposes. Support for legalization continues to grow and what was once taboo has become increasingly normalized and accepted.^{2–4} The legal market for marijuana grew to nearly US\$10 billion in 2017 and is projected to reach \$25 billion by 2021.⁵ Suppliers offer high-potency formulations such as edibles, extracts, and tinctures readily available in retail storefronts and the Internet.^{6,7} Marijuana has also emerged as a mainstream drug that approved patients' and consumers' use to alleviate symptoms of chronic pain, posttraumatic stress disorder, and opioid use disorder.^{8,9} This is despite the fact marijuana remains classified by the Controlled Substances Act as a Schedule I substance with no accepted medical use and a high potential for abuse.¹⁰ Looking forward, growth in availability and use across virtually every demographic group portend an urgent need to rapidly advance our understanding of this drug, its effects on people, and its potential for abuse and related harms.^{11,12}

Scope of Special Issue

Against this background of increasing availability and use of cannabis in the United States, the goal of this special issue is to explore new directions in cannabis research. The invited manuscripts target emerging topics and innovative methodologies required to keep pace with expanding use of cannabis in its many new forms by a much wider band of society. The growth and diversity of populations affected by cannabis underscore the ongoing need to understand the basic biology of natural and synthetic cannabis. Several study designs highlight the new data streams that can be leveraged to identify and characterize new segments of cannabis-using populations. Others illustrate novel uses of established data systems for addressing perennial substance abuse issues such as initiation of cannabis use during adolescence and the persistent effects that show up later in life. Studies in this special issue are broadly grouped into those that address basic biology, novel methods or data streams, and adolescent use of cannabis.

Specific Studies

Biology of exposure

Thomas et al reviewed the current knowledge of the interaction of natural and synthetic cannabis with biological substrates across the central and peripheral nervous systems and many other tissues, including the gastrointestinal tract and immune system cells. The wide distribution of CB1 and CB2 receptors in mammals produces widespread biological effects consequent to administration of both natural and synthetic cannabinoids. These widespread effects have proven to be a double-edged sword, indicating not only many potential therapeutic targets for cannabinoids (eg, appetite stimulation, cancer, and neurodegenerative disorders) but also undesirable off-target effects (eg, impaired learning and addiction). Recent decades of research have substantially increased our understanding of the biological effects of cannabinoids. Continued research will further our foundational knowledge of cannabis use and abuse and allow us to pursue the exciting potential to develop selective agents that are safe and effective treatments.

Lefever et al described the first evaluation of a device adapted to provide aerosolized exposure to cannabinoids in mice, opening up preclinical research to an approach that more closely reflects the most common route of administration of cannabis in humans (ie, smoking or vaping). This change in methodology is particularly important given that the current standard for animal model exposure is injection of cannabinoids, which may generate a greater role for first-pass metabolism, delay onset of effects, and miss alterations in cannabinoids that occur during heating in animal models compared with human users. Furthermore, some toxicologic or other health effects may occur only through inhalation. This study demonstrated that cannabinoids aerosolized by e-cigarette technology produce a profile of expected phenotypic effects, particularly for high-potency synthetic cannabinoids, and support use of this novel device in preclinical studies that may have greater translational relevance to human users.

Novel methods and data streams

"Big data" is a by-product of the conversion of record keeping and information exchange to electronic format and has become



a common way to explain the world around us. Not surprising then, several studies explored the utility of “big data” for cannabis research. Smiley-McDonald et al studied multidrug use among almost 200 000 pain management patients, a novel use of a large and abundant data source of clinical records accumulated in the normal course of drug testing of urine at pain clinics. The study results provide evidence of the growing number of people turning to cannabis on their own to relieve chronic pain with implications for treatment at the personal and public health levels. The potential of these large clinical data sets to help researchers understand cannabis use patterns and multidrug use is, as yet, barely tapped.

Barratt et al established the practical usefulness of a large, nonprobability survey (the Global Drug Survey [GDS]) to describe substance-abusing populations, detect in near real-time emerging trends of abuse, and inform the public health response to growing and sometimes life-threatening new drugs. Since 2015, GDS has administered in-depth surveys on drug use knowledge, attitudes, and behaviors to almost 100 000 or more drug users *each year*. While fully establishing the limitations caused by self-selection into epidemiologic studies, the authors provide compelling evidence of the power of the GDS to access a large and diverse sample, mirror the drug-using population, and reveal trends essential to designing timely and effective interventions.

Baumgartner et al leveraged a stochastic block modeling technique to analyze more than 2 million Twitter accounts to identify hidden populations of cannabis consumers in the San Francisco Bay Area. Multimode content analysis of the Twitter accounts formed a hierarchy of block groups with distinguishing and complex profiles of communities of illicit, recreational, and medical cannabis users. The resultant geo-social profiles have diverse practical applications in health care evaluation and creation of personalized messages in health promotion campaigns. The method frees public health initiatives from the time and expense of traditional data collection efforts to depict the target population and is easily scalable to large populations.

Peiper et al examined the emerging occupation of “bud-tender,” the staff who work at retail marijuana outlets commonly known as dispensaries. Dispensary staff stand at the intersection of unsubstantiated claims of panacea-like curative powers, an exponentially expanding consumer market afforded by Internet marketing, and the spirit of entrepreneurship in the United States. This study investigated how formally trained staff advise medical cannabis patients about the health and safety risks of a burgeoning number of legally available products. Although some states in the United States have started to establish requirements for formal training or qualifications for dispensary staff, this is all happening against a backdrop of conflicting federal and state laws. Among the social, occupational, and legal implications offered by their work, the authors shine a light on the critical role played by these 21st century drug dispensers in protecting the health and safety of consumers.

Hughes and Moxam-Hall took their research to the streets of Sydney, Australia, to study the utility of a smartphone application to prospectively monitor drug use and police encounters. In real time, subjects recorded their current location, the prevalence of illicit drug use around them, and the incidence and nature of police encounters. The ease of use reported by study subjects suggests that smartphone apps are a viable, economical, and timely option for registering the immediate extent and impact of illicit drug use. With appropriate analytic techniques, real-time reporting may potentially replace or supplement more costly and burdensome methods. The details of their development of the app and user reaction provide evidence-based guidelines to monitoring drug use in real time.

Freeman et al draw our attention to the long-studied issue of the relationship of substance use to resulting ill effects on physical and mental well-being. Focusing on an incarcerated population, Freeman et al relied on extant findings from the Multi-site Family Study on Incarceration, Parenting, and Partnering (MFS-IP) to illuminate these associations. Although their original intent was to identify special health needs that might be associated with frequent use of different types of illicit drugs, they found no difference by type of drug. Several regression model techniques were deftly used to assess the association of substance use with physical and mental health outcomes. Strong associations existed between drug use and problem conditions, whereas poor physical and mental health were not associated with the type of drugs used. The authors concluded that “. . . marijuana legalization will not affect the underlying myriad of social, environmental, and economic factors that affect inmates . . .” Their work provides a model for disentangling complex relationships between substance abuse and well-being that may counter conventional stereotypes about cannabis use.

Epidemiology of cannabis use in adolescence and young adulthood

Lower socioeconomic status (SES) of family of origin is known to be associated with numerous deleterious outcomes, including higher levels of cannabis use. However, families are embedded in a broader social context of schools and neighborhoods that define the “contextual” SES of youth. Milliren et al conducted a multilevel analysis of the association between contextual SES and cannabis use using data from the National Longitudinal Study of Adolescent to Adult Health (Add Health). The study found that each level of SES (family, school, and neighborhood) has significant associations with past 30-day cannabis use during adolescence and these associations persist into adulthood. These results suggest an expanded focus for intervention and prevention efforts beyond individual-level risk factors to lower SES schools and neighborhoods.

Although the epidemiologic study of cannabis use and associated use disorders has a long history in the United States, Forman-Hoffman et al provided new information on cannabis

initiation, use, and marijuana use disorders (MUDs) with a focus on young adolescents (aged 12–14 years). They used the National Survey on Drug Use and Health (NSDUH), which has the significant advantage of a large sample size ($N = 84\,954$) for analyzing less prevalent phenomena at these ages (eg, MUD) and may include a higher representation of high-risk youth compared with school-based samples. Results of particular interest include (1) the substantial increase in past year initiation from age 12 to 14 (0.9%–6.1%), (2) higher past year initiation in more recent survey years, and (3) the relatively high prevalence of rapid transitions from initiation of cannabis use to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*) marijuana use among young adolescence. Approximately one in six make this transition within the year of initiation. These results, and others in the study, highlight important covariates of cannabis use, initiation, and MUD among young adolescents and suggest focal points for prevention and intervention efforts.

Glasheen et al also used the NSDUH to investigate residential transience, a subset of residential mobility that focuses on populations with high levels of housing instability. Residential mobility during childhood has been linked to a number of poor mental health outcomes, including MUD and is expected to accentuate disruption of social networks and inhibition of educational attainment among adolescents and young adults. This study focuses more specifically on transience, which may have stronger associations with deleterious outcomes and be a more targeted focus for intervention. Overall residential mobility was associated with increased risk of cannabis use initiation but was more strongly associated with transience and limited to those under the age of 18. This first study to examine the association between residential mobility and cannabis initiation by age group highlights the potential importance of transience as an easily identifiable risk factor for focused prevention efforts.

Together, the articles in this special issue highlight advances in using alternative methods and data to better understand the changing phenomenon of cannabis use, products, and distribution in the United States. Future research will need to continue in these directions, from better emulation of human use of cannabis in animal model research, to leveraging a broader array of data and methods now available, to asking new questions using

established approaches. The United States is in the process of substantial changes in the legality and use of cannabis. Optimal support of policy, medical, and personal decisions regarding cannabis can only be helped by continued creative evolution of well-designed scientific research.

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