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Approaches to Measuring Cannabis Use in Injury Research: Beyond Drug Detection

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Abstract

Purpose of Review This review examines the challenges of measuring the effect of acute cannabis use as it relates to injury risk. This is relevant for researchers, particularly those studying drug-impaired driving, and practitioners such as those measuring impairment in workplaces or at the roadside.

Recent Findings Emerging research clarifies the challenges of linking drug levels of tetrahydrocannabinol (THC) in the body to the level of psychomotor and neurocognitive impairment, given individual differences in drug effects and tolerance. Without knowing more about the individual, such as information about the pattern of cannabis use, the levels of THC in the blood do not provide an indication of impairment, and therefore, do not indicate the relationship between drug use and injury risk.

Summary Future research should focus on measuring drug impairment, beyond drug detection, and identify novel ways of measuring impairment that have application for injury prevention.

Keywords Injury prevention · Cannabis impairment · Drug impaired driving · Measures of cannabis use

Introduction

In the USA and internationally, the legal status of cannabis has been changing rapidly over the past decade. Both policymakers and citizens seek policies that maximize benefits of more liberal cannabis policy while minimizing potential harms, with injury outcomes frequently cited as a concern. From an epidemiological perspective, understanding the existence and magnitude of injury-related risks from cannabis use must start with the fundamental question of measurement. The purpose of this review is to examine the challenges to measurement of cannabis use as it relates to injury risk.

There are many potential injury outcomes to be studied in relation to cannabis use, including the following: unintentional exposures, particularly by children, and/or overconsumption, by adults; violence including interpersonal and intimate partner violence; and impairment that may result in recreational, occupational, or motor vehicle-related injuries and fatalities [1, 2]. The evidence for associations between cannabis use and injury in each of these domains may come from a variety of sources such as hospital and trauma data, self-reported survey data, or poison center call data, police data collected at the roadside, or from controlled research studies. Given the strengths and limitations of each data source, a fuller understanding of the relationship between cannabis use and injury may require a triangulation of findings using various study designs and methodological approaches.

There are several challenges to understanding how the use of cannabis relates to injury risk and injury outcomes. Measurement of exposure to the main psychoactive component, tetrahydrocannabinol (THC), is complicated by factors including the concentration of THC in available products (ranging from a low percent THC to nearly 90% THC), other cannabinoid constituents (e.g., CBD), mode of use (e.g., vaporizing, dabbing, ingesting edibles), as well as potential interactions with alcohol or other drugs that

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could result in additive or multiplicative impairing effects. Even when considering the effect of a particular product, there are individual differences in pharmacokinetics, and the resulting impairment [3]. Finally, there is growing appreciation in recent years of the important role of an individual's tolerance to THC, which occurs after a pattern of frequent and regular use, and how tolerance mitigates the impairing effects of acute use [4, 5], and therefore may mitigate the risk of injury.

In this article, we consider the challenges to measurement of cannabis use, as it relates to injury risk with attention to the injury outcome being studied. Of note, there are two topics outside the scope of this review. First, we do not consider injury risks associated with the production of cannabis, such as explosions while making concentrated products, or occupational concerns in the cultivation of cannabis [6, 7]. Second, the focus of this review is on the acute use of cannabis, resulting impairment, and the risk of injury, and does not address how chronic use may increase risk, [8], beyond the consideration of how tolerance mitigates the effects of acute use. This review will highlight the limitations of biological samples for indicating drug impairment, especially the lack of correspondence between blood levels of THC and impairment, and the importance of considering tolerance to drug effect. We focus on impaired driving and motor vehicle crash risk as an illustration of those challenges in the extant literature.

Post-event Biomarkers

After an injury incident, such as a fall or collision, there may be biological samples that are taken from an injured person, or from others involved in the event, whether at an emergency department, worksite, or by a police officer, to determine the cause or contributing causes of the injury [9, 10]. There are several important considerations with biological samples. First, it is critical that studies be clear if they are using measures of Δ^9-THC (delta-9-THC), the primary psychoactive component of cannabis, or THC metabolites, such as THC-COOH (carboxy THC), which may be found in samples from blood or urine for days or even weeks after use. The presence of THC metabolites does not necessarily indicate impairment and may not even indicate recent use.

An additional consideration is the pharmacokinetics of THC — the way in which THC moves through the body. After inhalation of cannabis, which remains the most common mode of use [11, 12], the level of THC rapidly rise and peak within several minutes to about 10 min after use. Subsequently, the level of THC in the blood rapidly begins to fall [13, 14]. Meanwhile, the subjective drug effect and impairment continues to rise and remain for several hours. The relationship between blood levels and impairment defies a commonsense notion, informed by the familiar model from alcohol, that a higher level in the blood should equate to more impairment. Instead, a correlation between the blood level and impairment does not exist for THC. The pharmacokinetics also vary by mode of use, with the timing of peak levels occurring earlier and higher for inhaled cannabis, as compared to ingested cannabis [15].

Depending on the circumstances of an injury, such as when there is a motor vehicle crash, there may be limited information available about the timing of cannabis use before the event, or timing from the injury to when a biological sample is taken. There may have been a detectable level of THC at the time of the injury, which may no longer be detectable at the time a blood sample is obtained (with the exception of a fatality). However, there may be instances where more information is available. For example, in cases of pediatric unintentional exposures, it may be possible for a caregiver to report how much cannabis was consumed by the child, the mode of use (often ingested [16, 17]), and the time from exposure to receiving care at a hospital. Together, this information can lead to more complete understanding of the relationship between cannabis use and the resulting poisoning.

Beyond Blood Levels

Much of the extant literature on THC in biological samples has focused on blood, either whole blood or plasma. Collecting a blood sample is relatively invasive and requires specialized equipment and training, and thus has limited applications in injury prevention or enforcement. Thus, some researchers and policymakers have looked to oral fluid (salvia) or breath sampling as a more portable and less invasive alternative to blood [18, 19]. (Urine is of little use in determining acute impairment given the inability to detect delta-9-THC but is useful in detecting recent use on the order of days to weeks.) However, the same limitations exist for these matrices as do for blood [20]. Specifically, the level of Δ^9-THC in saliva or breath does not indicate the degree of impairment.

Although blood levels and other biological samples are relatively unhelpful at identifying impairment, they may hold more promise for indicating recent use. Identifying recent use would still be of value in injury prevention for settings in which no psychoactive or impairing substances should be used, such as occupational settings with safety sensitive tasks. Emerging research is considering how metabolite ratios and less commonly detected metabolites such as CBG may be used to indicate recency of use [21–23].

Tolerance

With regular and repeated use of cannabis, an individual will develop tolerance to some effects [4, 5]. Although the parameters of use resulting in tolerance are not fully determined, the pattern of use would need to be approximately daily, with heavier use resulting in greater tolerance and tolerance occurring faster [4]. In recent years, researchers and policymakers have recognized the importance of tolerance, and attention has turned to the extent that individuals may be tolerant to neurocognitive, psychomotor, and physiological effects of acute cannabis use [4, 5]. There has also been recognition that when considering individuals may have tolerance to some effects, policies based on a specific level of THC in a biological sample are not useful for differentiating a degree of impairment [24].

Tolerance to cannabis may not be a rare occurrence. Self-reported survey data indicate that nearly half of adults who report current cannabis use do so with a pattern of daily or nearly every day. For example, in a population-based survey of Colorado adults, 48% of those who reported any cannabis use in the past 30 days reported they used daily or nearly every day [11]. In a national Canadian survey, 19% of those who had used cannabis in the last 12 months used it on a daily basis [25]. Thus, a sizeable proportion of the population that uses cannabis does so with a frequency that could lead to some level of tolerance. Taken together, the complexities of the pharmacokinetics of delta-9-THC and tolerance make it challenging to identify recent cannabis use in the absence of additional self-reported information about the characteristics of the product used, timing of use, and prior pattern of cannabis use. An appreciation for the limitations of blood levels and other considerations is growing in the literature.

Illustration of Measurement Challenges: Cannabis and Motor Vehicle Crash Risk

Perhaps the best example of measurement challenges can be seen in the efforts to understand how cannabis use impacts motor vehicle crash risk. A large body of epidemiological literature has used fatal motor vehicle crash data, from the USA and internationally, to calculate the risk of a crash from cannabis use. In the USA, the data system is called the Fatality Analysis Reporting System (FARS). In the event of a fatal crash, states routinely collect blood samples for toxicology testing. States vary in their compliance, but ideally states would report all fatal crashes to FARS, which is then available to policy makers, practitioners, and researchers. FARS data have been used in numerous publications, which have in turn been used in meta-analyses generating an odds ratio for the crash risk associated with cannabis use [26–29]. However, FARS is subject to the challenges previously described: measuring metabolites versus delta-9-THC, and little to no information about mode of use, timing since use, tolerance to cannabis, or degree of impairment due to cannabis. Despite recognition that the FARS data system has significant limitations [30], this surveillance system continues to be used in cannabis-related injury research [31, 32]. Researchers choosing to use FARS data in this way must carefully consider the important limitation that detects the presence of a THC metabolite in the blood of a driver involved in a crash. Without knowing more information about pattern of use and recency of use, these data provide very little information about the contribution of acute cannabis use to a crash.

There are two ways that flawed measurement would result in bias, operating in opposite directions. Principally, this is because FARS data indicates the presence of either THC or its cannabinoid metabolites as one variable. When this variable is used in the analysis, it potentially includes a large number of people who have not used recently and were not experiencing a drug effect while driving. If one considers the prevalence of cannabis use in fatally injured drivers, use of this variable would overestimate the relationship between acute cannabis use and crash risk. However, in culpability studies, it could potentially bias the effect towards the null because culpable and non-culpable drivers would both be overidentified as having used cannabis.

Studies of crashes that specifically measure delta-9-THC are also likely to have a biased estimate of the effect of cannabis use on crash risk. Given the pharmacokinetics of cannabis, in that there is rapid uptake of the lipophilic molecule from the blood into organs like the brain, the levels in the blood may be very low or even non-detectable, despite recent use resulting in substantial impairment. If the individual were to be in a crash (whether fatally injured or not), they may not be identified as someone who recently used cannabis, thus underestimating the effect of recent cannabis use on crash risk. This is most likely to be the case in individuals without a pattern of frequent use. This may be someone who uses cannabis occasionally, perhaps socially.

Given the pharmacokinetics of cannabis, these same studies are likely to have a proportion of individuals who use cannabis frequently and may have tolerance that results in less impairment from the drug, but these individuals would be most likely to be found positive for the presence of THC. Any effort to identify a dose–response relationship between THC levels and crash risk, using these data would be unlikely to find one because the individuals most likely to have high levels of THC are the individuals least likely to be impaired or culpable for a crash. On the other

hand, individuals with low or non-detectable levels could be the most impaired and go unidentified. It is difficult to say how these sources of bias stack up with each other. Perhaps informed by this epidemiologic literature that is subject to the attributional problems just described, many states have policies setting a per se or permissible inference level for THC in the blood as a marker of impairment. In practice, however, there is little utility of a blood level for indicating impairment.

Measuring Impairment

To put it simply, the critical measurement challenge is not drug detection, but rather, measuring the degree of impairment. Laboratory settings and experimental designs offer the best opportunity to gain thorough measures of cannabis use and impairment associated with cannabis use. Researchers can recruit participants with particular characteristics, such as infrequent use, or daily use, to isolate acute effects in the absence or presence of tolerance [33–35]. Often these studies utilize within-subject designs, to compare individual performance after cannabis use to the participant's baseline level. Impairment is assessed with a range of laboratory measures. Some research has focused on neurocognitive or psychomotor outcomes including short-term memory, reaction time, and measures of executive function, and balance [33, 35, 36]. Other research has looked at brain-related changes such as those using fNIRS or EEG [37, 38]. More proximal to preventing motor vehicle injuries, a large body of literature has used observational and experimental designs to examine how acute cannabis use affects performance in driving simulators or in on-road studies [39]. A useful review of this literature is the recent meta-analysis by McCartney and colleagues, which thoroughly investigates the acute effects of THC on driving performance and relevant cognitive measures [39]. This review also illustrates the growing evidence for the importance of considering the role of tolerance.

Despite the contributions from experimental studies to our understanding of impairment, there are limitations worth noting. One key limitation is the use of within-subject designs where the outcome measure is compared before to after cannabis use, and change is interpreted to be a sign of impairment. However, there is currently lacking a clinical standard or threshold for many of the laboratory measures that would clearly indicate the presence or absence of impairment. For example, in simulator studies, standard deviation of lateral placement (SDLP) is often used as a marker of impaired driving performance. The use of this outcome is based on research with alcohol-impaired driving, and the degree of change that is shown after the consumption of alcohol use [40]. Although it considered predictive of crash risk [41, 42], it is an indirect measure of actual crash risk. Driving simulators offer a proxy for real world driving, which is a complex and variable behavior, and challenging to fully replicate in a laboratory. Further research may clarify the extent to which driving performance in a simulator translates to crash risk in real-world conditions and better model the conditions that differentiate a crash from a near crash event. A second important limitation of experimental and laboratory studies is they do not provide insights into the estimate of the prevalence of injury risk or effects of changing policy. They may help elucidate the mechanisms and conditions of impairment, but do not estimate the prevalence of impairment during activities like daily driving, or the public health burden of cannabis-related injuries.

Conclusion

Understanding the associations between cannabis use and injury outcomes is likely to remain an important topic as cannabis legalization is implemented in a growing number of places. Recent research has shown that measurement of delta-9-THC in blood or other biological samples is insufficient to establish impairment. New directions that pursue measurement of neurocognitive and psychomotor impairments relevant to the injury outcome being studies (e.g., reaction time, measures of executive function) will be critical in the development of methods to reliably detect and deter injuries that may be related to cannabis impairment. In the meantime, we urge researchers, policymakers, and the public to understand the limitations of existing efforts focused on THC measurement in biological samples and strive for policies that do not overemphasize blood levels. As revenues from legal cannabis sales in legalized areas reach new highs, ensuring adequate resources for research and development of accurate and unbiased cannabis-related impairment measurement tools will be important for protecting public health and safety.

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Declarations

Ethics Approval and Consent This is a review article, and no human subject review is required.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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