DRIVER BEHAVIOR & PERFORMANCE

TECHNICAL REPORT

FOUNDATION FOR TRAFFIC SAFETY

Cannabis Use, Public Health, and Traffic Safety: Outcomes from the Scientific Literature and Expert Opinion on the Potential Impacts of Rescheduling

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Title

Cannabis Use, Public Health, and Traffic Safety: Outcomes from the Scientific Literature and Expert Opinion on the Potential Impacts of Rescheduling

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Foreword

Legislative proposals in the United States, such as the Cannabis Administration and Opportunity Act, and the more recently proposed Rescheduling of Marijuana from the Drug Enforcement Administration, aim to remove cannabis from the list of Schedule I drugs under the Controlled Substances Act. The Drug Enforcement Administration proposal would change cannabis to Schedule III, in acknowledgement of its current accepted medical use and lower potential for abuse than other Schedule I and II drugs.

Efforts to liberalize cannabis, including at the federal level, should be appropriately informed about the impacts on public health, including traffic safety. While research on the crash risk associated with acute and chronic cannabis use has been equivocal, it has been clearly demonstrated that cannabis can impair a person's ability to drive safely, and emerging research on the effects of liberalizing cannabis use, including by the AAA Foundation for Traffic Safety, portends negative implications for traffic safety. This report synthesizes and consolidates the existing scientific evidence regarding cannabis use and public health and offers expert opinion on the potential impact of the proposed rescheduling, providing an accessible reference for interested stakeholders.

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About the Sponsor

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List of Abbreviations and Acronyms

AAAFTS	AAA Foundation for Traffic Safety
ABCD	Adolescent Brain Cognitive Development
ADHD	Attention deficit hyperactivity disorder
AIDS	Acquired immunodeficiency syndrome
BAC	Blood Alcohol Content
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CBD	Cannabidiol
CBN	Cannabinol
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease caused by the SARS-CoV-2 virus
CUD	Cannabis Use Disorders
DRE	Drug Recognition Expert
DRUID	Driving under the Influence of drugs, alcohol, and medicines
DUI-C	Driving under the influence of cannabis
ECS	Endogenous cannabinoid system
ED	Emergency Department
EVALI	Electronic cigarette, or vaping product use-associated lung injury
FARS	Fatality Analysis Reporting System
HIV	Human immunodeficiency virus
HLDI	Highway Loss Data Institute
IACP	International Association of Chiefs of Police
IIHS	Insurance Institute for Highway Safety
MML	Medical marijuana law
MSB	Male sexual behavior
NASEM	National Academies of Sciences, Engineering, and Medicine
NDAA	National District Attorneys Association
NTIS	National Technical Information Service
PIRE	Pacific Institute for Research and Evaluation
PTSD	Post-traumatic stress disorder
RML	Recreational marijuana law
SCRAs	Synthetic Cannabinoid Receptor Agonists
TGCT	Testicular germ cell tumor
THC	Delta-9-tetrahydrocannabinol
TIRF	Traffic Injury Research Foundation
U.S.	United States
WHO	World Health Organization

Executive Summary

Cannabis is currently a Schedule I controlled substance under the Federal Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act). The Drug Enforcement Administration has an ongoing process to consider moving cannabis to a Schedule III drug, thereby reducing the associated penalties. Arguments have been made in recent years inviting public support for rescheduling and legalization of cannabis in the United States.

In 2017, a committee of experts gathered by the National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that there was a lack of scientific research regarding the health effects of using cannabis and cannabis-derived products. Much more modest in scope, the current report endeavors to provide a picture of the current state of scientific knowledge on the impact of cannabis use as it is associated with the factors established by the Controlled Substances Act for drug scheduling.

This report included two main tasks. Part I offers a detailed review of the literature, including a description of the approach used to build the review; a brief portrayal of the biological mechanisms by which cannabis components affect (or could affect) human health and behavior; and a summary of findings with references. Additionally, key takeaways are presented in non-academic layman terms. Part II involved focus groups with subject matter experts, who shared their opinion on the potential impacts of cannabis rescheduling on public health and traffic safety.

For the literature review, using the 2017 NASEM report as the starting point, the research team conducted a search of the literature using a variety of scholarly and scientific databases as well as a review of resources available from professional associations and organizations. The results of the search were synthesized and summarized, and were aligned with factors considered under the Controlled Substances Act: Pharmacology, Potential for Abuse, and Public Health Impacts.

This review of the literature was complemented by two focus groups of 14 expert panelists who brought together various viewpoints about future public health and traffic safety scenarios that may occur should the rescheduling of cannabis to be approved. The invitees had expertise in multiple public health arenas that might be impacted by the rescheduling of marijuana on the federal level and included representatives from organizations and agencies that have an interest in the topics of marijuana use and related policy.

In general, most of the experts agreed that the main concern coming from the rescheduling relates to how the public would perceive the rescheduling. Panelists were concerned that the public would perceive the rescheduling as an indication that "*it [cannabis] is safe*," increasing the likelihood that cannabis-related negative health and safety consequences would develop. On the other hand, participants agreed that the rescheduling would allow researchers to fully study the public-health consequences of cannabis, as federal restrictions on the type and strength of cannabis allowed to be used in federally funded research has limited the types of research that can be conducted. Experts also suggested that cannabis rescheduling would have an impact on traffic safety—that rescheduling could translate into an increase in the unsafe use of cannabis among drivers. The experts overwhelmingly supported continued research to understand both the use of cannabis alone, as well as its cognitive impact and impairment associated with driving. Participants also supported research to develop more tools to assess impairment and continued training efforts for law enforcement officers who are evaluating impairment during a roadside stop.

Introduction

The term cannabis refers to a genus of the family Cannabaceae, which includes species that together are commonly known as marijuana (e.g., sativa, indica, and ruderalis), as well as the many strains that have surfaced by hybridization and crossbreeding. This report will not make any distinction between these species and the terms cannabis and marijuana are used interchangeably.

Cannabis is currently a Schedule I controlled substance under the Federal Comprehensive Drug Abuse Prevention and Control Act (the Controlled Substances Act). There is an ongoing process by the Drug Enforcement Administration to consider moving cannabis to a Schedule III drug, thereby reducing the associated penalties, and arguments have been made in recent years inviting public support for rescheduling and legalization of cannabis in the United States. Some of these arguments include (a) suggesting that cannabis use is less harmful than alcohol, tobacco, and opioids; (b) suggesting that criminal offenses related to cannabis use would cause more harm than the cannabis use itself; and (c) legalizing the recreational use of cannabis would eliminate the illicit market, allow for regulated access and use by the public, and allow for an increase in government revenue through taxation (Hall & Lynskey, 2020).

In 2017, a committee of experts gathered by the National Academies of Sciences, Engineering, and Medicine (NASEM) was tasked with conducting a comprehensive review of the evidence regarding the health effects of using cannabis and cannabis-derived products. The 2017 NASEM report concluded that there was a lack of scientific research on the subject, which "*has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively"* (NASEM, 2017, page 1).[1]

Much more modest in scope, this report does not attempt to update the comprehensive 2017 NASEM report, but to use the 2017 NASEM report as a starting point to provide a picture of the current state of scientific knowledge on the impact of cannabis use as it is associated with the factors established by the Controlled Substances Act for drug scheduling.

This report is organized as follows. Part I offers a detailed review of the literature, including a description of the approach used to build the review; a brief portrayal of the biological mechanisms by which cannabis components affect (or could affect) human health and behavior; and a summary of findings with references. Part I concludes with a summary of the literature review findings presented in non-academic, layperson's terms. Part II presents expert opinion on the potential impacts of cannabis rescheduling on public health and traffic safety gathered via focus group discussions with subject matter experts.

[1] As the current project was nearing completion, NASEM released a report titled *Cannabis Policy Impacts Public Health and Health Equity (*NASEM, 2024). Diverging from the 2017 NASEM effort and this current effort focused on the state of knowledge on cannabis use and public health, the complementary 2024 NASEM report provides a review of cannabis regulatory frameworks and recommended actions to minimize public health harms at the federal and state levels.

Part I: Review of the Literature

Part I is organized as follows. First, a summary characterizes cannabis components and the most popular cannabis products. Next, a summary background of the issues around the scheduling of drugs in the United States (U.S.) is provided. This is followed by a description of the approach followed by the research team in building this report. Finally, the findings are presented, including a section highlighting the current challenges in cannabis research.

Cannabis Components

Broadly speaking, the components of cannabinoids are divided into three categories: (1) endocannabinoids, which are mainly synthesized by animal organisms, (2) phytocannabinoids, which are biosynthesized in the cannabis plant, and (3) synthetic cannabinoids, which are prepared in the laboratory and have similar or complete physiological characteristics as phytocannabinoids and endocannabinoids.

The cannabis sativa plant has more than 100 different cannabinoids, including delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN). These phytocannabinoids work by binding to cannabinoid receptors, as well as other receptor systems (Rock & Parker, 2021).

Cannabis Products

There is a proliferation of cannabis products in the U.S. market, which are based on hybrid varieties defined by their psychoactive and medicinal effects, appearance, taste, potency, or odor and come in a variety of forms (e.g., edibles, flower, concentrates). Although smoking cannabis has been the most popular mechanism for cannabis use (Smart et al., 2017; Schauer et al., 2020), edibles—cannabis-infused food and drink products—are accounting for proportions of legal U.S. cannabis sales. (Miller and Seo, 2021) (Peterson et al., 2023). Inhaled cannabis products are marketed with flavors, tastes, and smells (Watkins et al., 2023; Gammon et al., 2021).

Compared with inhaled cannabis, edible cannabis has a slower onset of effects, although edibles often have a longer lasting high. Overall, the subjective effects of inhaled cannabis peak at approximately 15 to 30 minutes and last for about 2 to 3 hours, whereas the effects of ingested (edible) cannabis products peak between 1 to 3 hours and can last up to 8 hours (Blake and Nahtigal, 2019; Chen and Rogers, 2019; Okey, 2023).

Although a process to flavor cannabis was first recorded in the 19th century (Crocq, 2020), only recently has flavored cannabis become popular in the U.S., particularly in states with recreational marijuana laws (RMLs) (Watkins et al., 2023; Chaffee et al., 2023). Tobacco research has demonstrated that flavors in tobacco products decrease harm perception and increase product appeal. Subsequently, it has been posited that flavors of inhaled cannabis products may have a similar effect and impact cannabis initiation or dependence (Watkins et al., 2023). Recent studies present evidence that flavored cannabis increases its appeal to users. Compared with older adults, males, and white individuals, flavored cannabis use was higher among younger adults, females, and black and Latinx cannabis users (Watkins et al., 2023). On the other hand, research has found no association between cannabis flavor and individuals' motivation to quit (Glasser et al., 2022).

Drug Scheduling Factors

Marijuana is currently recognized by the U.S. Drug Enforcement Agency under the Controlled Substances Act as a Schedule I controlled substance. In making decisions regarding the scheduling of a drug, the following factors about the drug should be taken into account. (21 USC 811: Authority and criteria for classification of substances):

- Its actual or relative potential for abuse.
- Scientific evidence of its pharmacological effect, if known.
- The state of current scientific knowledge regarding the drug or other substance.
- Its history and current pattern of abuse.
- The scope, duration, and significance of abuse.
- What, if any, risk there is to public health.
- Its psychic or physiological dependence liability.
- Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

For simplicity in this report, the Controlled Substances Act factors are grouped into three related and sometimes overlapping categories: Pharmacology, Abuse, and Public Health Impact.

Pharmacology

Pharmacology is the study of the nature, effects, and uses of drugs (Canadian Centre on Substance Use and Addiction, 2017). The basic processes that pharmacology studies focus on are how drugs get into the body, what they do in the body, how they do it, and the ways in which the body breaks down and gets rid of them. In other words, how a drug interacts with the body and how the body interacts with the drug (Canadian Centre on Substance Use and Addiction, 2017). The review of this category includes scientific evidence of the pharmacological effects of cannabis, if known, and the state of current scientific knowledge regarding cannabis.

Abuse

In 21 U.S.C. 802, the Controlled Substances Act refers to the assessment of "potential for abuse," "addiction-forming or addiction-sustaining liability," and "dependence," but does not define these terms. In 2017, the Food and Drug Administration issued a document titled "Assessment of Abuse Potential of Drugs," which defined drug abuse as "the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect (euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood);" it defines potential of abuse as "the likelihood that abuse will occur with a particular drug product or substance with central nervous system (CNS) activity" (Food and Drug Administration, 2017). For brevity and simplicity, under this category we included a review of cannabis' "actual or relative potential for abuse," "its history and current pattern of abuse," and "the scope, duration, and significance of abuse."

Impact on Public Health

The impact of problem drugs on public health can be varied (Lo et al., 2020; WHO, 2019), involving domains such as heredity, biology, psychology, cognitive science, family, social development, and cultural structures (Lo et al., 2020). This report reviews the impact of cannabis both as a cause of negative outcomes, as well as its therapeutic potential. For brevity and simplicity, this category includes a review of whether cannabis is a "risk to the public health, if any," its "psychic or physiological dependence liability," and "whether it is an immediate precursor of a (another) substance already controlled" under the Controlled Substances Act.

Methods

Using the 2017 NASEM report as the starting point, the research team conducted a review of the prolific literature covering the wide range of topics and issues under study. To manage the review of such a vast amount of literature and make the report feasible and useful, the review included the following:

First, seminal publications and reports, published since 2016, referring to the three Controlled Substances Act factors under review were identified, including systematic reviews. This first step informed about the prevailing state of knowledge in the selected Controlled Substances Act factors, up until the date each publication was published.

This was followed by a review of primary research published since the seminal reviews were issued. In areas where no systematic review was identified, all relevant primary research published after August 2016 was reviewed.

In conducting the review, the following databases were searched: PsycInfo, PsycNET, Compendex, National Technical Information Service (NTIS), Web of Science, PubMed, Google Scholar, and the Transport Research International Documentation, RoSAP, as well as publications from professional associations and organizations (e.g., IIHS-HLDI, TIRF, GHSA, Responsibility.Org, NDAA, IACP), and U.S. and state government reports. Studies that covered the U.S. as well as any other country in which marijuana has been decriminalized and/or legalized were considered (e.g., Canada, Uruguay, and Thailand).

Multiple keywords were entered within relevant domains (e.g., impairment, decriminalization, legalization, risk perception, crash risk, law enforcement, toxicology, and prosecution) and subdomains (e.g., marijuana products, potency, cannabis detection), and applicable keywords to those domains and subdomains were searched using "AND" and "OR" operators. Additionally, forward and backward searching was conducted on related articles and reports identified in the citations listed that might have been missed in the initial database searches. Each article was reviewed by the research team to determine its relevance for this project. Irrelevant documents were excluded.

Next, the articles and documents were searched, focusing on specific domains:

- Within the "Pharmacological Effects" Controlled Substances Act category, the focus was how cannabis products work inside the human body to facilitate the description and understanding of the outcomes associated with cannabis products, whether detrimental or favorable.

- Within the "Actual or Relative Potential for Abuse" Controlled Substances Act category, the focus was short-term, acute effects as well as long-term effects of cannabis use, including factors associated with dependency and whether cannabis is a precursor for the abuse of other drugs.
- Within the "Impact on Public Health" Controlled Substances Act category, the focus was the impact of cannabis on the following outcomes: cancer, respiratory diseases, cardiovascular diseases, mental health, injuries (traffic safety–related and other injuries), as well as a review of miscellaneous outcomes such as oral health, renal function, and sexual behavior, among others.

It was clear that conducting a complete and comprehensive review of each one of the vast number of papers and studies associated with the use of cannabis would not be feasible for this study. As indicated, this challenge was met by focusing initially not on individual papers, but on systematic reviews of scientific importance published since 2016. The scientific relevancy of the reviews was identified by looking at the number of times the review was cited by other authors, including specific references to the reviews made by more recent publications. The number of citations naturally declined for reviews conducted in more recent years. In some novel research areas, less than a handful of reviews were published. In those cases, individual studies were reviewed.

Challenges in Conducting Cannabis Research

The results of this review highlight some of the complexities involved with cannabis research in the U.S. To a large extent, these complexities arise from important challenges researchers in the field have faced. This section lists some of the most common limitations in conducting cannabis research or in comparing outcomes across different studies.

- **Cannabis legal status.** Since cannabis is an illegal product, it is difficult for some researchers to study the drug in detail (NASEM, 2017).
- **A large variety of cannabis products.** The type of cannabis product, as well as the specific compounds that are consumed, can affect behavior and health outcomes. The lack of uniformity that exists in cannabis products makes it difficult to obtain consistent research outcomes (Dor, 2022).
- **Biphasic effect.** The evaluation of health-related impacts of cannabis is further complicated by the biphasic effect profiles associated with cannabis use (i.e., a low dose of cannabis may produce one effect—for example, a reduction in anxiety— while the opposite—increased anxiety—would take place at a high dose) (Borodovsky & Budney, 2018; NASEM, 2017).
- **Unclear frequency and chronicity of use.** The frequency and chronicity of use of a particular cannabinoid or combination of cannabinoids can also have an impact on health-related outcomes. (Borodovsky & Budney, 2018; NASEM, 2017).
- **Beneficial/therapeutical effects may be temporary and/or hide deeper problems.** Some research has reported therapeutic benefits among cannabis users with mental health problems; however, THC (like alcohol, stimulants, or opioids) can temporarily reduce pre-drug negative mood states (relief from negative emotional states such as depressed mood), providing an apparent immediate relief, but without resolving the underlying cause of mood disturbance. Apparent initial therapeutic effects may increase vulnerability to cannabis use and contribute to the development of substance use disorders among individuals with mental disorders (Borodovsky & Budney, 2018; NASEM, 2017; Klein & Clark, 2022).

- **Reverse causality.** Finding there is an association between cannabis and health outcomes does not necessarily mean that cannabis causes that outcome. For some health issues such as mental health outcome, cannabis can either be a source or a consequence of the disease (WHO, 2016; Hall and Pacula, 2010).
- **Uncontrolled and unmeasured factors.** The presence of confounding factors can bias cannabis research (e.g., tobacco use among cannabis smokers) (Hall and Pacula, 2010; NASEM, 2017; Blest-Hopley et al., 2020; WHO, 2016).
- **Unaccounted differences in THC:CBD ratio among the products under study.** The discrepancy in findings from memory-related studies may be associated with differences in the THC:CBD ratios of the products used in those studies (Mechoulam et al., 2002).

Results

The following sections summarize key findings from the review, which are presented by (a) their relevancy to the Controlled Substances Act factors under review and (b) subcategories within each Controlled Substances Act factor, as follows:

Cannabis Pharmacology

Cannabinoids act primarily through the endogenous cannabinoid system (ECS): a vast network of chemical signals and cellular receptors located throughout the brain and body, which regulates many critical tasks and functions such as learning, memory, emotional processing, sleep, pain control, and immune responses (Bridgeman & Abazia, 2017; Piscura et al., 2023).

The ECS is stimulated by endocannabinoids, molecules produced by the human body that share structural similarity with molecules in the cannabis plant called phytocannabinoids (WHO, 2016; Borodovsky & Budney, 2018; Piscura et al., 2023).

Two receptors are particularly relevant to the metabolism of cannabis: CB1 and CB2:

- CB1 receptors are primarily in the brain, largely concentrated in regions involved in memory, emotional responses, cognition, motivation, and motor coordination (Piscura et al., 2023; WHO, 2016).
- CB2 receptors are found primarily in the body. They play a role in the regulation of the immune system and act on the gastrointestinal tract, liver, heart, muscle, skin, and reproductive organs (WHO, 2016).
- Recent research also indicates that in addition to acting on CB1 and CB2 receptors, THC and CBD can also interact with other receptors activated by the ECS. The possibility that the interaction between cannabis and non-CB receptors may play a role in cannabis' addictive behaviors. Further research on this topic is needed (Pintori et al., 2023).

THC

THC, the main cannabinoid with psychoactive properties, binds to the CB1 receptor to exert its psychoactive effect. Research has found that acute administration of THC is reinforcing in humans regardless of whether or not CBD is co-administered. Also, CB1 receptor antagonists have been found to precipitate withdrawal in mice that have been exposed to THC (Schlag et al., 2021).

CBD

Unlike THC, CBD has a low affinity for the CB1 receptor. Further, CBD appears to be a negative allosteric modulator of CB1 (i.e., it slows or inhibits the binding of THC components to CB1). Subsequently, CBD does not produce acute intoxication, has been proven to treat refractory epileptic syndromes in children, and may have anti-inflammatory, anxiolytic, and antipsychotic indications (Bridgeman & Abazia, 2017; Pennypacker et al., 2022; Hidding et al., 2023).

Synthetic Cannabinoids

Synthetic cannabinoids, also called synthetic cannabinoid receptor agonists (SCRAs), are non-phytocannabinoid or endocannabinoid agonists for CB1 and/or CB2 (Breivogel & Pulgar, 2023; NASEM, 2017).

SCRAs also bind to CB1 and/or CB2 cannabinoid receptors. They were originally developed as research tools aimed at investigating the endogenous cannabinoid system and/or to develop potential clinical therapies (Piscura et al., 2023). Like phytocannabinoids, SCRAs are also lipophilic compounds that show pharmacokinetic properties typical of lipophilic drugs (Piscura et al., 2023).

Compared with THC, the majority of SCRAs are highly potent, binding with a 10 to 100 times higher binding affinity at the CB1 receptor (Piscura et al., 2023).

The set of SCRAs is a constantly evolving subset of compounds that have undergone several changes over time (Amaral et al., 2023; Piscura et al., 2023).

Routes of Administration

The route by which cannabis is used can impact the onset, intensity, and the addictive potential and negative consequences associated with use (Bridgeman & Abazia, 2017; Kluemper, 2022; NASEM, 2017). Although smoked cannabis tends to produce greater effects immediately, edibles tend to produce greater delayed effects (Okey, 2023; Kluemper, 2022; NASEM, 2017).

Smoking. Overall, THC is rapidly transferred from lungs to the blood during smoking, with the effects of smoking cannabis reaching their maximum after 15 to 30 minutes and typically disappearing within 2 to 3 ½ hours (Bridgeman & Abazia, 2017); however, there is a high inter-subject variability due in part to variations in factors such as duration of intake, inhalation volume, inhalation device, and performance level on the task at hand (Preteroti et al., 2023). In their review of the literature, McCartney and colleagues (2021) reported that the impact of inhaled cannabis on some driving tasks may last 5 hours or more, depending on the THC dose and other factors.

Vaping. Cannabis vaping onset, peak, and duration are similar to those of smoking cannabis (NASEM, 2017). Vaping is increasingly prevalent among young adults, particularly in states with

RMLs (Harrell et al., 2022). In their 2022 review, Harrell and colleagues (2022) reported that despite its increase in use, cannabis vaping is still less prevalent than nicotine vaping. Because vaporization tends to provide effects similar to smoking, but with a reduced exposure to the byproducts of combustion, it was suggested that compared with smoking cannabis, vaping may have some benefits (Bridgeman & Abazia, 2017; Fischer et al., 2022; Preteroti et al., 2023); however, there are different types of vaporization devices and products, carrying different levels of risk (MacCallum et al., 2023; NASEM, 2017). Research on the alleged positives and negatives of vaping is lacking. Almost nothing is known about the long-term impact of vaporized cannabis on the respiratory system and the possibility of the downstream development of lung diseases (Preteroti et al., 2023).

Oral Ingestion. Orally ingested cannabis has an initial pass in the liver, which reduces the effective dose compared to inhalation (Kluemper, 2022). Following oral ingestion, psychotropic effects manifest within 30 to 120 minutes, reach their maximum effect after 2 to 3 hours, and last for about 4 to 12 hours, depending on the dose (Bridgeman & Abazia, 2017; NASEM, 2017). Edibles have been associated with the ingestion of excessive amounts of cannabis as well as with elevated rates of pediatric injuries (NASEM, 2017).

Distribution, Accumulation, and Half-Life

The majority of cannabinoids are very lipophilic compounds that readily distribute into the brain and adipose tissue (Kluemper, 2022). THC and CBD have a half-life (i.e., the time required for the concentration of the drug to reach half of its original value) that is biphasic (i.e., the curve that the drug concentration follows presents two separate parts, a steep portion and a shallow portion of the curve) (Preteroti et al., 2023). The initial phase distributes THC to highly vascularized tissues, such as the lungs, heart, brain, and liver. After being absorbed, cannabinoids distribute to less vascularized tissues (e.g., adipose tissue) where they accumulate and are subsequently released. The release of cannabinoids from adipose tissue can take place for weeks after consumption (Preteroti et al., 2023; Kluemper, 2022).

The route of administration affects cannabis pharmacology. After oral intake, THC goes to the liver where it is metabolized into 11-hydroxy-THC (psychoactive) and then into 11-COOH-THC (not psychoactive), or is eliminated. Although 11-hydroxy-THC can be formed after consumption of THC from inhalation (vaping, smoking) as well as from oral use (by mouth, edible, sublingual), levels of 11-hydroxy-THC are typically higher when eaten compared to inhalation (Huestis et al., 1992). After inhalation, THC enters the bloodstream quickly through the lungs, with the peak blood concentration achieved within 6 to 10 minutes after inhalation (Chayasirisobhon, 2020). As a result, peak THC concentrations are lower after oral than smoked administration, but conversely 11-hydroxy-THC/THC ratios are higher after oral than smoked cannabis (Schwilke et al., 2009).

Regarding cannabis half-life, THC has an initial and brief half-life of 4 hours (the steep part of the curve), and a terminal half-life of 25 to 36 hours (the shallow part of the curve). CBD has an initial half-life of 1–2 hours and a terminal half-life of 18 to 32 hours (Preteroti et al., 2023)

Cannabinoids and their metabolites eventually are eliminated in the urine and feces, a process that that can be prolonged due to the highly lipophilic nature of cannabinoids (Kluemper, 2022). Chronic users redistribute inactive metabolites from adipose tissue into blood and urine, which is the underlying reason for positive urine drug screens weeks after last use and prolonged half-lives of different compounds (Kluemper, 2022).

Cannabis Used in Conjunction with Alcohol

The combined use of cannabis and alcohol may result in greater psychoactive toxicity than either substance alone.

Heavy alcohol and cannabis use during adolescence can contribute from small to moderate disruptions in brain structure and function (Lees et al., 2021); however, the underlying mechanisms behind this outcome remain unclear (Zou et al., 2022).

Both cannabis and alcohol have been shown to interact through the ECS (Wolfe et al., 2022); however, although cannabinoids primarily act via the ECS, ethanol interacts with a variety of different molecular substrates that act on a variety of neurochemical processes (Wolfe et al., 2022).

Besides the psychoactive toxicity of a combined alcohol and cannabis use, researchers have posited that cannabis could be used to treat individuals with alcohol use disorders; however, research on this possibility is lacking (Wolfe et al., 2022; Gendy et al., 2023).

Cannabis Used in Conjunction with Tobacco

Very little is known about the pharmacology of combined use of nicotine and cannabis. Tobacco smoking has been associated with lower CB1 receptor levels, which suggests that tobacco smokers may be less sensitive to the effects of THC (Nasrin et al., 2023; Hindley et al., 2020). Recent research showed that CBD and its active metabolite have an inhibitory effect on nicotine (Nasrin et al., 2023).

Although research suggests cannabis and tobacco could each be used to counter the effects of the other, more research is needed before any therapeutic recommendation can be formulated (Hindley et al., 2020).

Cannabis Potential for Abuse

Cannabis use can have acute (short-term) as well as chronic (long-term) effects on human health. According to the WHO (2016): **"**The short-term effects of cannabis use are those that can occur shortly after a single occasion of use; while long-term health effects are those that arise from regular cannabis use—especially daily use—over periods of months, years or decades."

Acute Effects

Although there is wide inter-individual variation, cannabis can produce a range of acute dose-dependent effects, including intoxication, euphoria, memory impairment, psychotomimetic effects (i.e., production of symptoms that are similar to those of psychosis), anxiogenic effects (causes anxiety), attention deficits, and tachycardia (elevated heart rate) (Lawn et al., 2023). As described in the 2017 NASEM report, acute cannabis intoxication has been associated with enhanced sensitivity to colors and/or music, altered perception of time, decrease in short-term memory, dry mouth, impaired perception, and impaired motor skills (NASEM, 2017). Cannabis can impair memory, attention, and psychomotor functions, although the most robust effects were reported for verbal learning and working memory (Wickens et al., 2022).

Although the risk of death due to cannabis overdose is extremely small compared to the risks of opioid and stimulant drug overdoses, this risk increases when it occurs conjointly with traumatic physical injury, or in individuals with cardiac pathologies. (WHO, 2016; Rock et al., 2022).

Chronic Effects

Daily consumption of cannabis (THC) can produce persistent chronic impairments in memory and cognition, particularly when cannabis use begins in adolescence. It has been suggested that these effects arise because daily use of cannabis can reduce the number of CB1 receptors over time (WHO, 2016).

The 2017 NASEM study reported that there is substantial evidence that frequent cannabis users are more likely to develop schizophrenia or other psychoses and moderate evidence of a small increase in the risk for developing depressive disorders and social anxiety disorder (NASEM, 2017).

The majority of research conducted on the long-term impact of cannabis on human health has focused on THC. Very few studies looked at long-term effects associated with CBD. The few studies that looked at repeated CBD administration do not report tolerance development (i.e., the need for higher doses to achieve a therapeutic effect over time). Further, CBD does not appear to be converted to THC in humans (Kluemper, 2022).

Dependence

The Food and Drug Administration (2017) defines "physical dependence" as *"a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug."* The Food and Drug Administration (2017) defines "psychological (or psychic) dependence" as *"a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug."*

The factors described below have been associated with progression to dependence on cannabis.

Potency. Over the past four decades cannabis potency (its percentage of THC) has on average doubled worldwide (Hall & Lynskey, 2020; WHO, 2016; Englund et al., 2017; NASEM, 2017). Consumption of high-potency cannabis has been associated with depression and anxiety, but the effect and the evidence is weak (Petrilli et al., 2023). The evidence is stronger for an association between the consumption of high-potency cannabis and greater adverse psychological outcomes and dependence (Englund et al., 2017; Smart et al., 2017; Petrilli et al., 2023; Schlag et al., 2021; NASEM, 2017). The 2017 NASEM study, as well as more recent reviews, report that individuals who use higher potency cannabis are more likely to be diagnosed with a psychotic disorder[2] and/or

[2] The National Institute of Mental Health refers to psychosis as a collection of symptoms that affect the mind, where there has been some loss of contact with reality. Behavioral signs for psychosis may include among others: Suspiciousness, paranoid ideas, or uneasiness with others; trouble thinking clearly and logically; withdrawing socially and spending a lot more time alone; decline in self-care or personal hygiene; disruption of sleep, including difficulty falling asleep and

have a relapse compared with those who have never used cannabis (NASEM, 2017; Petrilli et al., 2023). On the other hand, the association with psychotic disorders was not usually found to be significant among users of low potency cannabis (Petrilli et al., 2023).

Co-morbid Presence of Various Psychological and Mental Health Factors. Progression to cannabis dependence is related to factors such as intensive use of cannabis and early onset of use. Contributors to the progression to dependence also include psychological and mental health factors such as low self-esteem, self-control, and coping skills. Cannabis dependence tends to occur more often among individuals who report any lifetime psychiatric, mood, anxiety, conduct, and/or personality disorder; as well as those with attention deficit hyperactivity disorder (ADHD) (Hall & Lynskey, 2020; WHO, 2016; Schlag et al., 2021; NASEM, 2017).

Heavy Use and Early Onset. The 2017 NASEM study reported that the rate for developing cannabis dependence one year after onset of use was about 4 percent (NASEM, 2017). As indicated, the risk of cannabis dependence increases with the use of high-potency cannabis strains, heavy amounts consumed, high-frequency use (heavy, daily), and early onset of that use, starting in adolescence (Schlag et al., 2021).

Some researchers, however, have questioned the strength of these findings, arguing that research often ignores potentially confounding factors such as genetic predispositions and environmental factors (e.g., family history, socio-cultural-economic status, and past life-experiences), as well as polysubstance abuse. Failure to account for these factors weakens the examination of the long-term causality hypothesis (Pintori et al., 2023).

Flavored Products

As previously mentioned, flavored cannabis is becoming increasingly popular in the U.S. (Watkins et al., 2023; Chaffee et al., 2023) and it has been posited that flavors in inhaled cannabis products may contribute to cannabis initiation and/or dependence (Watkins et al., 2023); however, evidence for such association is unclear (Glasser et al., 2022).

THC:CBD Ratio

Altogether, CBD seems to dampen the deleterious cognitive effects of THC exposure, suggesting that cannabis with a relatively low THC:CBD ratio may be less likely to have adverse effects than cannabis with a high THC:CBD ratio; however, the evidence is mixed (Englund et al., 2023; Pintori et al., 2023). Some studies found that while high doses of CBD may reduce the deleterious properties of THC, low doses of CBD could potentiate THC's intoxicating effects (Solowij et al., 2019; Pintori et al., 2023).

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reduced sleep time; emotional disruption; anxiety; lack of motivation; and/or difficulty functioning overall (National Institute of Mental Health, 2023).

Polysubstance

Polysubstance use is common among cannabis users (Hasin & Walsh, 2020). Cannabis is the most commonly used drug among those who use alcohol (Hasin & Walsh, 2020; Gorfinkel et al., 2021; De Aquino et al., 2019).

Cannabis as a Gateway Drug

Almost 50 years ago cannabis was proposed to be a "gateway drug" for alcohol, tobacco, and other illicit drugs (Kandel, 1975); however, the 2017 NASEM report, as well as more recent reviews, found no evidence in support of the gateway hypothesis (Sabia et al., 2021; Jorgensen and Wells, 2021; NASEM, 2017). Although some sequencing in drug use may exist, sequencing does not imply causality. And although there is an association between marijuana use and hard drug use, this can largely be explained by other factors (Jorgensen and Wells, 2021).

Recent studies not only reject the gateway hypothesis but indicate that cannabis initiation before the onset of tobacco and/or alcohol use is rare (Cho et al., 2021; Cohn & Elmasry, 2023). Using data from the Population Assessment of Tobacco and Health study, Cohn and Elmasry (2023) recently reported that cannabis initiation occurring before alcohol or tobacco use was uncommon (6%) and not more prevalent than trying either alcohol or tobacco first, with alcohol use often tried before cannabis or tobacco.

Not only there is little evidence in support of an association between cannabis and other drugs' initiation, but also regarding other drug use in general. The 2017 NASEM report concluded that evidence that cannabis use changes the use and patterns of use of other substances is limited (NASEM, 2017).

Stronger (moderate) is the association between cannabis use and the development of substance dependence and/or a substance abuse disorder for alcohol, tobacco, and other illicit drugs (NASEM, 2017). Recent reviews report that individuals with cannabis use disorders (CUD)[3] often also show alcohol use disorders, opioid use disorders, and/or nicotine dependence (Hasin & Walsh, 2020; Gorfinkel et al., 2021; De Aquino et al., 2019).

RMLs and Polysubstance Use

A recent review by Farrelly and colleagues (2023) reported that studies examining the association between RMLs and concurrent cannabis and alcohol use showed inconsistent and/or contradictory results. The review reported that the evidence for an association between RMLs and tobacco use is even more limited than that for RMLs and concurrent cannabis and alcohol use (Farrelly et al., 2023).

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[3] According to WHO (2016), cannabis-use disorders refer to a spectrum of clinically relevant conditions and are defined via psychological, social, and physiological criteria to document adverse consequences, loss of control over use, and withdrawal symptoms. Cannabis-use disorders are defined in the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013) and in the International statistical classification of diseases and related health problems (ICD-10; WHO, 1992). ICD-10 distinguishes between harmful and dependent use of cannabis, while in DSM-5 cannabis-use disorders are classified by the severity of health impairments into mild, moderate, and severe disorders.

Tolerance

As reviewed by Ansell and colleagues (2023), the frequency of cannabis use can have an impact on the ECS, including the downregulation of CB1 receptors (Curran et al., 2016; Ramaekers et al., 2009). Frequent use of cannabis may lead to tolerance of the impairing effects of THC on cognition and psychomotor function (Ansell et al., 2023). Some frequent cannabis users may not develop tolerance at all, or develop it only for some performance domains (Colizzi and Bhattacharyya, 2018).

Recent work has revealed prominent sex differences in the acute response and tolerance of cannabinoids in both humans and animal models (Piscura et al., 2023), with females developing tolerance of the pain-relieving effects of THC more readily than males (Matheson & Le Foll, 2023; Cooper & Craft, 2018).

Tolerance Breaks. A tolerance break, or T-break, has been proposed as a strategy for managing cannabis use. A T-break generally involves a self-directed process of abstaining from cannabis for a predetermined amount of time. Unlike attempts to quit, T-breaks are generally done without the desire to quit, with the primary goal of reducing tolerance levels so that a smaller amount of cannabis would be needed to achieve the same high when cannabis use is resumed (Fontana et al., 2022; Ansell et al., 2023). A recent review of online sites serving cannabis users found that the recommended length of time for the T-breaks varies considerably (from 2 to 4 weeks), although no sound scientific basis exists for these durations (Ansell et al., 2023). There is a dearth of scientific research on the topic. Furthermore, for some cannabis users, taking a T-break may be a marker of increased risk for problematic outcomes (Ansell et al., 2023).

Potential for Abuse Among Population Subgroups

Racial/Ethnic Minorities. The 2017 NASEM study reported differences in the prevalence of cannabis use in the U.S. across racial/ethnic groups, with Black Americans having the highest rate of cannabis use (10.7%), followed by non-Hispanic whites (8.4%) and Hispanics (7.2%) (NASEM, 2017). These figures changed after the enactment of RMLs, particularly among Hispanics and non-Hispanic whites, and among those aged 21 years or more (Martins et al., 2021). Despite differences in prevalence, research is unclear on whether cannabis-related risk and/or the presence of protective factors varies across racial/ethnic groups. (Stoa, 2022; Rafei et al., 2023).

One of the motivations for cannabis legalization was to reduce racial inequalities regarding the disproportionate incidence of arrests and convictions of minorities for cannabis-related charges. Although arrests for cannabis-related offenses have declined since multiple states have legalized marijuana, that may not be the case with convictions and incarcerations. Overall, it is too early to assess the wider impact of legalization on racial/ethnic minorities. (Hall & Lynskey, 2020; Kavousi et al., 2022; Stoa, 2022; Rafei et al., 2023)**.**

Older Adults. The 2017 NESAM report concluded that there was no sound evidence linking older age with a risk or a protective factor for developing problem cannabis use (NASEM, 2017). Following the trend towards legalization of cannabis in multiple states, there has been an increase in its use among individuals ages 50+, mainly due to a combination of medical and quasi-medical reasons (Wolfe et al., 2023; Hall & Lynskey, 2020). Although cannabis use may help individuals with medical problems (e.g., to assist with sleep, control pain, stimulate appetite), compared with younger individuals, older users may be at a higher risk of some adverse health effects, such as car

crashes, confusion, dizziness, falls, and delirium. As a result, the benefit/risk ratio that cannabis poses for older users remains unclear (Hall & Lynskey, 2020; Riggs & Thant, 2022).

Sex. Animal and human evidence indicates that compared with males, female use of cannabis is associated with the reinforcing and/or rewarding effects of cannabis at lower doses, which in combination with a faster development of tolerance could lead to rapid escalation of cannabis problems among individuals assigned female at birth (Matheson & Le Foll, 2023). That said, sex-related biological influences on responses to cannabis are still not fully understood. Furthermore, sociocultural factors may also play a significant role in determining trajectories of cannabis use (Matheson & Le Foll, 2023; Cooper & Craft, 2018). The 2017 NASEM report reported that in the U.S., males were about twice as likely (10.6%) to use cannabis as females (NASEM, 2017).

Impact on Public Health

This section summarizes the extant scientific knowledge on the association between cannabis use and health outcomes.

Cancer

Research has shown that cannabinoids can have both anticancer as well as pro-tumorigenic effects.

Respiratory Cancers. Laboratory-based research suggested that like cigarette smoking, cannabis smoking could be associated with cancers of the lung and the upper aerodigestive tract (de Groot et al., 2018). Despite this concern, most epidemiological studies have failed to clearly demonstrate a causality between cannabis use and cancer of the lung, yielding mixed results (WHO, 2016; Ghasemiesfe et al., 2019; de Groot et al., 2018; Thandra et al., 2021; NASEM, 2017). The 2017 NASEM review concluded that overall, there was moderate evidence suggesting no association between cannabis smoking and the incidence of lung cancer (NASEM, 2017).

The failure of epidemiological studies to yield a clear assessment of risk could have been attributed to methodological research limitations (de Groot et al., 2018), such as difficulties in getting a proper population control (e.g., by only examining cancer patients) (WHO, 2016); by failing to clearly document participants' exposure to cannabis and/or failing to control for tobacco use and other confounding effects (Hall and MacPhee, 2002; de Groot et al., 2018; Ghasemiesfe et al., 2019; NASEM, 2017).

Other Upper Aerodigestive Tract Cancers (Head and Neck). The evidence regarding the association between cannabis use and the risk of head and neck cancer has also lack consistency (Hall & Lynskey, 2020; WHO, 2016), with some of the studies reviewed by the WHO in 2016 reporting an increasing risk (e.g., (Zhang et al., 2015), others a reduction in risk (e.g., (Liang et al., 2009), and others no association at all (e.g., (Aldington et al., 2008). As with respiratory cancer, the 2017 NASEM review concluded that overall, there was moderate evidence suggesting no association between cannabis use and the incidence of head and neck cancers (NASEM, 2017).

In a review conducted by Ghasemiesfe and collegues (2019), the authors concluded that either the evidence reported by most of the studies was insufficient for a clear interpretation of results, or the study showed a moderate-to-high level of methodological problems.

Bladder Cancer. Experimental research has suggested that THC can interact and exhibit cytotoxic activity[4] against bladder cancer (Anis et al., 2021), and that THC *"can potentially exert synergistic effects when combined with other agents*" (Whynot et al., 2023); however, as with respiratory cancer and head and neck cancer, the 2017 NASEM review concluded that the moderate evidence available suggested no association between cannabis use and the incidence of bladder cancer (NASEM, 2017). So far, the limited research on the subject has shown contradictory findings (Mehrnoush et al., 2022; Thomson et al., 2023).

Brain Cancer. The 2017 NASEM review reported that there was no evidence for an association between cannabis use and the incidence of glioma (a type of brain tumor), or of an association between parental cannabis use and the incidence of neuroblastoma in their children (NASEM, 2017). On the other hand, reviews by Ghasemiesfe and colleagues (2019) and very recently by Chandy and colleagues (2024), identified two studies reporting an association between monthly cannabis smoking and the development of glioma, but the studies were either hampered by methodological constraints and/or in need of further research (Ghasemiesfe et al., 2019; Chandy et al., 2024).

Skin Cancer. The 2017 NASEM review reported that there was no evidence for an association between cannabis use and the incidence of Kaposi sarcoma, a type of skin cancer (NASEM, 2017). In their review, Ghasemiesfe and colleagues (2019) noted that a prospective study published in 2009 found that marijuana use among HIV-infected white men was associated with a risk for developing Kaposi sarcoma (Chao et al., 2009); however, Ghasemiesfe and colleagues (2019) pointed out that the study failed to account for the level of exposure to cannabis, or to report separately for marijuana-only smokers.

Testicular Germ Cell Tumor (TGCT). The 2017 NASEM review reported that there was limited evidence for an association between cannabis use and the incidence of TGCT (NASEM, 2017). The reviews by WHO (2016) and Hall and Lynskey (2020) reported moderate evidence of an association between cannabis use and testicular cancer. Studies reviewed by the WHO in 2016 reported estimated odds ratios for cannabis users between 1.7 and 2.3, (Daling et al., 2009; Lacson et al., 2012; Trabert et al., 2011). In a more recent review, the authors reported evidence of an association between TGCT and cannabis, but only among individuals with more than 10 years of marijuana use (Ghasemiesfe et al., 2019). The Ghasemiesfe et al. (2019) review indicated a higher confidence for the outcome of TGCT studies than for other cancer-related studies. A reason for such a relatively high confidence level is that, since tobacco use is not known to be associated with the occurrence of testicular cancer, no potential confounding by tobacco smoking had confounded the TGCT research.

Other Cancers. A few studies examined whether there is an association between marijuana ever use and breast cancer, colorectal cancer, melanoma, and non-Hodgkin lymphoma (Ghasemiesfe et al., 2019). These studies failed to detect any of these associations; however, methodological concerns limit interpretation of these studies (Ghasemiesfe et al., 2019).

Cannabis Antitumor Properties. The 2017 NASEM review reported that although cannabinoids have been found to have anticancer activity in cell lines and animal models, there is some evidence for the possibility that cannabinoids can be an effective treatment for cancers, although the evidence was limited (NASEM, 2017). A recent review by Hanganu and colleagues

[4] Cytotoxic denotes a substance or process that can damage cells.

(2022) reiterated the need for well-designed human studies to investigate the efficacy and safety of using cannabinoids for treating cancers. The review pointed out that "the anticancer properties of cannabis must be balanced against their immunosuppressive properties, which may have pro-tumorigenic effects." A similar warning was reported by Guggisberg and colleagues (2022, 24) in their recent review: "…most published, peer-reviewed case reports provide insufficient data to support the claim for cannabis as an anticancer agent, and should not be used in place of evidence-based, traditional treatments outside of a clinical trial."

Respiratory Diseases (Other Than Cancer)

Similarities between the process of smoking cannabis and tobacco (i.e., both processes involve the inhalation of the desired biologically active compounds along with toxic combustion products) raised concern for the acute impact of cannabis smoking on the development of diseases that have already been associated with tobacco use, such as airway inflammation, chronic bronchitis, or emphysema (Tashkin & Roth, 2019).

Some differences in the effects of tobacco and cannabis on health have been established however. For instance, while tobacco smoking produces acute bronchial constriction, cannabis smoking causes acute bronchial dilation, depending on the dose of THC (NASEM, 2017; WHO, 2016). The association between chronic respiratory symptoms and regular smoking of cannabis is less clear (Tashkin & Roth, 2019).

Chronic Obstructive Pulmonary Disease (COPD). COPD, the fourth-leading cause of death worldwide, is a progressive disease that is known to produce decreases in lung function among tobacco smokers (WHO, 2016; NASEM, 2017). Studies focusing on cannabis smoking as a cause of COPD found that although cannabis smokers do tend to display symptoms linked with COPD, such as cough, sputum, and wheezing, it is unclear whether cannabis smokers are at a higher risk of COPD than non-smokers of cannabis. Such a lack of clarity is largely due to methodological research limitations (WHO, 2016; Martinasek et al., 2016; Hall & Lynskey, 2020; NASEM, 2017; Tashkin & Roth, 2019; Preteroti et al., 2023).

Asthma. Asthma is a respiratory disease sharing many similarities with COPD. Like with COPD, there is no clear evidence for an association between cannabis use and either asthma risk or asthma exacerbations, largely also due to methodological limitations, such as failure to control for important confounders such as adherence to the use of asthma medications (NASEM, 2017; Preteroti et al., 2023).

Lung Infections. Cannabis smoking can affect the function of key immune cells participating in the lung's defense against infection. This has raised concern that cannabis smokers could be at an elevated risk of developing primary infections (pneumonia), particularly when using cannabis products containing impurities (WHO, 2016; Preteroti et al., 2023); however, the 2017 NASEM review reported there was no evidence for an association between cannabis use and adverse immune responses in healthy individuals (NASEM, 2017). Cases of bullous lung disease (pathologically enlarged air spaces in the lung) have been reported among cannabis smokers (WHO, 2016); however, methodological limitations have also precluded assessing causality from these reports (Tashkin & Roth, 2019). Research on this issue is still lacking (Preteroti et al., 2023).

Electronic Cigarette, or Vaping Product Use-Associated Lung Injury. As indicated, it was suggested that when compared with smoking cannabis, vaping cannabis may present some benefits. In 2019 however, a surge in cases observed among e-cigarette or vape users presenting

symptoms such as dyspnea, cough, fever, constitutional symptoms, gastrointestinal upset, and hemoptysis[5] was observed. This symptomatology was termed Electronic cigarette, or Vaping product use-Associated Lung Injury, or EVALI for short (Soto et al., 2023). It was found that EVALI occurrence was linked with the liquid used in the vaporization process (the e-liquid), which typically contains ingredients such as psychoactive agents (e.g., nicotine, THC), solvents, and flavoring compounds, all ingredients with potential health risks (e.g., toxic/chemical induced lung injury) either alone or in combination. The addition of Vitamin E acetate (a thickening agent for THC) to the e-liquid has been a major contributor to the EVALI risk (Overbeek et al., 2020). In their review, Harrell and colleagues (2022) pointed out that being young, cannabis vaping, higher frequency of cannabis vaping, and obtaining products from informal sources were risk factors for EVALI. Unfortunately, a clear understanding of EVALI risk is lacking. For instance, a study by Boakye and colleagues (2022) reported that state-level cannabis vaping prevalence was not positively associated with the incidence of EVALI. Research on this issue has been challenged by difficulties with the identification of the sources of THC (with informal sources associated with an elevated risk of EVALI) and because different cannabis vaporization devices and products carry different levels of health risk (MacCallum et al., 2023).

Secondhand Smoking. Research has established that there is a close relationship between second-hand tobacco smoke and negative health outcomes. Subsequently, there is concern that second-hand cannabis smoking may also have a negative impact on individuals' health (Goodwin et al., 2023; McKee et al., 2018). Concern is particularly high for children, where accidental exposures to cannabis are increasing (Riggs & Thant, 2022). Unfortunately, research on the impact of second-hand cannabis smoking on individuals' health has been lacking.

Among the few recent studies using the Adolescent Brain Cognitive Development (ABCD) Study, Wade and colleagues (2023) examined the impact of second-hand cannabis exposure on cognitive performance in children ages 10 to 13 years old. They reported that secondhand cannabis was not related to cognition after controlling for sociodemographic factors.

Children and the Accidental Ingestion of Cannabis

The 2017 NASEM review pointed out that the increasing availability, diversity, and potency of cannabis products have elevated the drug's potential for accidental injuries and death. Indeed, children's accidental exposure to cannabis is increasing (Riggs & Thant, 2022). The 2017 NASEM review reported that the accidental ingestion of cannabis by young children can result in respiratory failure and coma (NASEM, 2017). Recent data also indicate that hospitalizations of children after cannabis ingestion are typically brief and according to a 2022 review, deaths have not been reported (Riggs & Thant, 2022).

Cardiovascular Diseases

Tachycardia (Elevated Heart Rate). The CB1 and CB2 cannabinoid receptors are both found in the cardiovascular system. Cannabis (THC) use can produce rapid changes in cardiovascular function (e.g., an increase followed by a decrease in heart rate), as well as changes in vascular contractility (ability of the heart muscle to contract), but the effects are generally mild and not life-threatening (Pabon et al., 2022). These symptoms have been reported largely in heavy daily

[5] Hemoptysis is when blood is coughed up from the lungs.

cannabis smokers but may be less pronounced among young individuals. Studies conducted in controlled settings showed that young users of cannabis can develop tolerance to the tachycardia effects within 2 to 4 weeks of cannabis use (WHO, 2016). Recent research has also shown that symptomatic tachy- and brady-arrhythmias[6] can appear among cancer patients using cannabis (Laish-Farkash et al., 2023). Although laboratory and retrospective analyses have found evidence suggesting that cannabis may have a negative impact on the cardiovascular system, prospective clinical data has not confirmed these suggested findings (Ghosh and Naderi, 2019).

Myocardial Infarction. Early research suggested that harmful cardiovascular effects occurred only in people with pre-existing heart disease. The 2017 NASEM report concluded that there was limited evidence of an association between cannabis use and the occurrence of acute myocardial infarction (NASEM, 2017).

More recent research, however, reported on case studies showing that acute exposure to cannabis, even by young healthy people, may lead to myocardial infarction, stroke, and other severe cardiovascular events (Weresa et al., 2022; Hall & Lynskey, 2020). Despite these case studies, reports based on large national databases as well as cohort-based studies show conflicting results, largely due to methodological limitations (Theerasuwipakorn et al., 2023). A recent meta-analysis of 20 studies and over 183 million patients conducted by Theerasuwipakorn and colleagues (2023) found that cannabis use failed to predict a major cardiovascular adverse event. Nevertheless, the authors warned about the soundness of these findings and reiterated the need for clarifying research.

Secondhand Smoking and Cardiovascular Disease. Laboratory studies have suggested that like secondhand tobacco use, secondhand cannabis smoking may have an impact on vascular endothelial function[7] (WHO, 2016); however, despite this biological plausibility, epidemiologic evidence remains unclear (Middlekauff et al., 2022).

Stroke. The 2017 NASEM review reported that the association between cannabis use and the incidence of stroke was unclear (NASEM, 2017). Some research indicated that cannabis-associated strokes tended to occur mainly among chronic cannabis users, or when cannabis users also smoked tobacco (WHO, 2016). More recent research reports that the cannabis–stroke causality is still unclear (Ochoa, 2021; Pérez-Neri et al., 2023).

On the other hand, it has been suggested that cannabinoid activation of the CB1 receptor may trigger a neuroprotective effect, albeit this suggestion has been debated and needs evaluation (Pérez-Neri et al., 2023).

Mental Health

Cannabis-Use Disorders. The 2017 NASEM review reported that early onset of cannabis use as well as frequent use of cannabis increase the likelihood an individual can develop CUDs (NASEM, 2017). Compared with individuals with no CUDs, those with past-year or lifetime CUDs

[6]Tachyarrhythmias are irregular heart rhythms that cause the heart to beat faster than the normal resting rate, while bradyarrhythmias are slower than typical.

[7] The endothelium intervenes in the regulation of blood fluidity and platelet aggregation, as well as in immunology processes.

can be at a higher risk of psychosis, mood disorders, anxiety disorders, and personality disorders, although the association between CUDs and other disorders is unclear (Hasin & Walsh, 2020).

Depression. Activation of the CB1 receptor by cannabinoids may have an impact on individuals' moods. Cannabis users commonly report that they use cannabis to help with their depression; however, some longitudinal studies indicated that cannabis use (particularly heavy cannabis use) was associated with increased risk for subsequently developing depression. The 2017 NASEM review reported that cannabis use did not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder (PTSD) (NASEM, 2017).

The direction of the cannabis-depression relationship is unclear, with opposite causal directions being possible (i.e., having a major depressive disorder increasing the risk of cannabis initiation, and vice versa) (Borodovsky & Budney, 2018). Unfortunately, the cannabis use–depression relationship is hard to assess, for it is usually mediated by associations with other substance use disorders (Blanco et al., 2016). Although research on the impact of cannabis on depression is equivocal, cannabis use has been more often associated with an increased, rather than decreased risk of depression (Borodovsky & Budney, 2018).

Anxiety.[8] Cannabis use can elicit acute episodes of intense anxiety as well as exacerbate symptoms of anxiety among those with an anxiety disorder (Borodovsky & Budney, 2018). Together with panic attacks and agoraphobia, anxiety is one of the most commonly acute symptoms linked to the use of cannabis (Padoan et al., 2023). These symptoms can occur particularly among relatively infrequent cannabis users (<10 cannabis uses per month), after they use increasingly more potent cannabis (Borodovsky & Budney, 2018).

Daily cannabis use was also associated with developing an anxiety disorder later in life. Individuals with cannabis dependence have been found to show elevated comorbidity with anxiety disorders (Padoan et al., 2023); however, the direct causal connection between cannabis use and anxiety is unclear. The 2017 NASEM review reported that cannabis use did not appear to increase the likelihood of developing depression, anxiety, or PTSD (NASEM, 2017). Like with depression, reverse causality (anxiety motivating the use of cannabis; cannabis causing anxiety) is possible. (Borodovsky & Budney, 2018). Some researchers have suggested that the impact of cannabis on anxiety may vary by sub-type of anxiety disorder (Walsh et al., 2017), being more associated with elevated incidence of social anxiety (Blanco et al., 2016; Feingold et al., 2016) but not for other types of anxiety. Thus, the relationship between cannabis and anxiety is complex, like that between depression and cannabis use. Factors such as cannabis use history, cannabis potency, pre-disposition to an anxiety disorder, and consumers' ability to titrate (understand/measure/control) the dose they use may all affect the extent to which individuals experience the acute effects of cannabis as being anxiogenic (causes anxiety) or anxiolytic (relieves anxiety) (Borodovsky & Budney, 2018).

[8] Individuals with generalized anxiety disorder show symptoms such as chronic, pervasive anxiety and worry accompanied by nonspecific physical and psychological symptoms (e.g. restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbances) (DeMartini et al., 2019).

Post-Traumatic Stress Disorder.[9] The 2017 NASEM review reported that cannabis use did not appear to increase the likelihood of developing depression, anxiety, or PTSD (NASEM, 2017). As with depression and other anxiety disorders, the data are highly equivocal (NASEM, 2017), with most clinical studies suggesting a negative impact of cannabis use on PTSD outcomes (Borodovsky & Budney, 2018).

Schizophrenia[10] and Other Psychoses. The 2017 NASEM review reported that cannabis use is likely to increase the risk of developing schizophrenia and other psychoses (NASEM, 2017). Cannabis use has also been associated with worsening of existing symptoms of schizophrenia, particularly in sub-groups of the population with serious physical medical conditions (e.g., HIV, multiple sclerosis), as well as adversely impacting the clinical course (i.e., trigger relapse and outcomes for those with psychotic disorders) (Borodovsky & Budney, 2018).

The association between cannabis use and the development of a psychotic disorder appears to be dose-dependent, particularly for individuals at an increased risk (e.g., genetic vulnerability, exhibiting early signs or symptoms, earlier onset cannabis use) (Borodovsky & Budney, 2018). Regular use of high potency cannabis also appears to increase risk. (Borodovsky & Budney, 2018). Some studies have also indicated that the disease burden of schizophrenia is accentuated among individuals who start using cannabis during adolescence (Allebeck et al., 2023). Although the evidence suggests a modest contribution of cannabis to the development of schizophrenia, causality has been difficult to assess as it also can be explained by factors which could increase the risk of both cannabis use and schizophrenia such as genetic risk and/or childhood abuse (WHO, 2016).

Bipolar Disorder. The 2017 NASEM review reported that there was limited evidence of an association between cannabis use and the risk of developing bipolar disorder, and moderate evidence that cannabis use could increase symptoms associated with bipolar disorder (NASEM, 2017). Despite some recent studies linking cannabis use with bipolar disorder, recent reviews reiterated the limited knowledge in this field, and the need for more systematic studies (Walter et al., 2021; Maggu et al., 2023).

Regarding a potential therapeutic use of cannabis, a 2018 review reported no sound study showing cannabis and/or CBD to have potential as an effective therapeutic agent for bipolar disorder (Borodovsky & Budney, 2018).

Suicide Risks (Ideation, Attempts, Death). The 2017 NASEM review reported that there was moderate evidence of an association between cannabis use and an increased incidence of suicide ideation, attempts, and completion. The association between cannabis use and the incidence of suicide ideation and attempts is stronger among heavier users (NASEM, 2017).

More recent reviews agree with the 2017 NASEM report that there is evidence of an association between cannabis use and suicide risk (Denissoff et al., 2022; Shamabadi et al., 2023).

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[9] PTSD is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event, series of events or set of circumstances. An individual may experience this as emotionally or physically harmful or life-threatening and may affect mental, physical, social, and/or spiritual well-being (APA, n.d.).

[10] "Schizophrenia is a mental and behavioural disorder classified in the ICD10, which is characterized by distortions in thinking, perception, emotions, language, sense of self and behaviour. Common experiences include hearing voices and delusions" (WHO, 2016).

Nevertheless, the existing evidence is not yet rigorous enough to allow drawing conclusions on causality (Denissoff et al., 2022).

Social Cognition. Social cognition is a sub-domain of cognitive functioning that refers to a set of cognitive processes applied to the recognition, understanding, accurate processing, and effective use of social cues in real-world situations (e.g., correct recognition of faces, or of emotions).

The 2017 NASEM review reports there is only limited evidence of an association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles (NASEM, 2017). Recent reviews indicate that research on this topic is lacking (Bourque and Potvin, 2021; Fusar-Poli et al., 2023).

Cognitive Performance. The 2017 NASEM review reported that there was moderate evidence of an association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention (NASEM, 2017).

Several meta-analyses and reviews have been published within the past 5 years to examine the relationship between acute and chronic cannabis use and cognitive performance (McCartney et al., 2021; Zhornitsky et al., 2021; Figueiredo et al., 2020; Krzyzanowski & Purdon, 2020; Lovell et al., 2020; Platt et al., 2019; Scott et al., 2018; Dellazizzo et al., 2022). The most consistent cognitive impairment observed during acute cannabis intoxication was a decrease in performance on verbal recall tasks. A meta-analysis published in 2021 found moderate-to-large effects of acute cannabinoid exposure on both verbal learning and verbal memory (Zhornitsky et al., 2021). Regarding the chronic effects of cannabis on verbal episodic memory, research has examined the possibility that abstinence could lead to a complete recovery of verbal recall performance, but the evidence is mixed (Zhornitsky et al., 2021).

Injuries

Overall, injuries due to cannabis use are rare, but can occur when cannabis is used alone or with other substances, with the latter concern particularly high as a factor in motor vehicle crashes (Rao et al., 2018). While some of the studies noted do not deal directly with injuries, they offer insight into the conditions that could lead to injury (i.e., crashes).

Motor Vehicle Crashes. Laboratory studies, in particular studies using a driving simulator, have shown an association between cannabis and crash risk. Laboratory and simulator studies that have examined the effects of acute cannabis intoxication on driving performance have found that the psychomotor skills necessary for safe driving become increasingly impaired at higher doses of cannabis (Sewell et al., 2009). Driving failures (e.g., lane departures) after acute cannabis use were associated with frequency of use, occurring more often among occasional cannabis users than with daily users (Miller et al., 2022). Miller and colleagues speculated that such a difference may be related to tolerance and/or learning how to compensate for drug effects (e.g., by reducing speed).

When used together, cannabis and alcohol are associated with worse performances than when cannabis is used alone. The simultaneous use of alcohol and cannabis had a larger negative impact on drivers' visual function, although driving performance was only significantly affected by the higher alcohol dose (Ortiz-Peregrina et al., 2022). Further, drivers who often co-use cannabis and alcohol are more likely to engage in a variety of risky driving behaviors (Kelley-Baker et al., 2021).

Although laboratory experiments warn about the impact of cannabis on psychomotor performance, they do not necessarily reflect the complex nature of driving ability and motor vehicle crash risk attributed to driving under the influence of cannabis (DUI-C) in a real-world scenario. Epidemiological studies have been conducted to close this gap, however, they are showing mixed results (Hall & Lynskey, 2016; Blandino et al., 2022; Berning et al., 2015; Compton & Berning, 2009; Lacey et al., 2009; Rogeberg & Elvik, 2016; Brubacher et al., 2022; Sewell et al., 2009; Asbridge et al., 2014).

A common limitation of epidemiological studies is that cannabis users tend to have characteristics similar to those of other groups with a high crash risk, including being young, male, polysubstance users (alcohol in particular)—all factors that could confound results if not properly taken into account. Unfortunately, accounting for all these confounding factors in real-world, epidemiological studies is a daunting task.

What epidemiological studies have clearly shown is a sustained increase in the prevalence of THC among U.S. drivers, as revealed by the 2007 and 2013–2014 National Roadside Surveys (Berning et al., 2015). Further, despite the travel restrictions imposed during the COVID-19 pandemic, the proportion of drivers admitted to a trauma center following a crash who were positive for cannabis use increased (Rudisill et al., 2023).

The issue remains whether the well-documented increase in cannabis prevalence detected among motor vehicle crashed drivers denotes causality, or merely reflects an increase in use by the population (i.e., cannabis is increasingly detected among crashed drivers not because the drug caused the crashes, but because more drivers are using it).

In 2017, the NASEM review concluded there was "*substantial evidence of a statistical association between cannabis use and increased risk of motor vehicle crashes*" (NASEM, 2017). The 2017 NASEM report relied somewhat heavily on Rogeberg and Elvik's updated meta-analysis (Rogeberg and Elvik, 2016), which was the most recent and comprehensive systematic review on the topic of cannabis and crash-related risk that was available at the time. The NASEM committee agreed with the authors' conclusion that self-reported cannabis use or the presence of THC metabolite in blood, saliva, or urine was associated with 20 to 30 percent higher odds of a motor vehicle crash. The authors described the magnitude of this association as low to moderate in range.

The NASEM (2017) report also noted that Gjerde and Mørland (2016) challenged the Rogeberg and Elvik (2016) conclusion that there was only a moderately increased odds ratio of 1.22 or 1.36 for crash involvement during acute cannabis intoxication. Gjerde and Mørland (2016) argued that the authors misunderstood limitations that were present in previous studies (e.g., studies that failed to fully account for acute cannabis intoxication) and posited that the cannabis risk for crashes should be higher than those estimated by Rogeberg and Elvik (2016).

On the other hand, some of the studies included in the NASEM 2017 review were based on crash data from the Fatality Analysis Reporting System (FARS), a database that has been deemed unsuitable for drug-related analyses (Berning & Smither, 2014). The inclusion of these studies may have also biased the NASEM review.

The European Integrated Project DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) conducted roadside data collection across nine European countries to determine the prevalence of psychoactive substances in the general driving population. By merging the prevalence findings from the individual countries with hospital data, the authors built a de-facto crash-control

study and concluded that drivers faced a "slightly increased risk" when both alcohol was present in the blood alcohol content (BAC) range of 0.01 g/dL to < 0.05 g/dL and drivers were positive for THC (Hels et al., 2011).

To further examine the contribution of drugs to motor vehicle crashes, the U.S. National Highway Traffic Safety Administration (NHTSA) sponsored a direct case-control study examining drug and alcohol crash risk in Virginia Beach, Virginia (Compton & Berning, 2015; Lacey et al., 2016). The Drug Crash Risk study obtained biological measures on more than 3,000 crash drivers at the scenes of the crashes, and 6,000 control (comparison) drivers. Control drivers were recruited one week after the crashes at the same time, day of week, location, and direction of travel as the crash-involved drivers. Data included 10,221 breath samples, 9,285 oral fluid samples, and 1,764 blood samples. Oral fluid and blood samples were screened and confirmed for the presence of alcohol and drugs. The study reported an unadjusted odds ratio of 1.25 associated with the presence of THC. After adjusting for gender, age, race/ethnicity, and alcohol, the authors found no indication that any drug significantly contributed to crash risk. The adjusted odds ratios for THC were 1.00 [95% confidence interval: 0.83, 1.22], indicating no increased or decreased crash risk. The study also reported that when combined with alcohol, cannabis use increases crash risk; however, the joint contribution of cannabis and alcohol to crash risk was not significantly larger than that caused by alcohol alone, a finding coincidental with those reported by the European DRUID study (Hels et al., 2011).

Although the DRUID and NHTSA's Drug Crash Risk study both suggest a relatively minor contribution of cannabis to crash risk (unless cannabis is consumed simultaneously with alcohol), the findings from these studies do not rule out the possibility that cannabis could increase crash risk. Both studies faced limitations. The DRUID study was forced to merge data from jurisdictions with varying rules and enforcement procedures, with aggregated hospital information. The NHTSA study, although homogeneous and rigorous in design and application, was restricted to only one jurisdiction. Cannabis use and driving behaviors may differ in other jurisdictions. Further, the range of THC values obtained from participant drivers was not ample enough to allow for an estimation of crash risk under different THC concentrations (only presence vs. absence of the drug was analyzed).

More recently, NHTSA sponsored an examination of data on seriously injured roadway users from seven trauma centers and fatally injured crash victims presenting directly to medical examiners at four selected sites. The study found that active THC was the most prevalent drug (25.1%), followed by alcohol (23.1%), stimulants (10.8%), and opioids (9.3%). Overall, 19.9% of the roadway users were positive for two or more categories of drugs (Berning, 2022; Thomas, Darrah et al., 2022); however, as the authors pointed out, these findings show prevalence and raise concern for potential crash risk, but do not prove impairment.

Another approach to assess the contribution of cannabis to crash risk was based on pre/post legislation outcomes. Studies of this type examined the impact of medical marijuana laws (MML) and RMLs on the prevalence of DUI-C. Measuring self-reported perception, Fink and colleagues (2020) reported an association between MML and cannabis impairment. On the other hand, Ellis and colleagues (2022) estimated that the passing of MMLs was associated with a reduction in health expenditures related to motor vehicle crashes by almost $820 million per year. Regarding RMLs, pre/post studies in Washington State reported an increase in the proportion of fatal-crash-involved drivers who were THC-positive, but causality was unclear (Tefft & Arnold, 2020; Tefft et al., 2016; Hansen et al., 2020; Tefft and Arnold, 2021). A recent study conducted in Washington State (Voy, 2023) also reported an increase in crashes after enacting a RML, but largely

on less severe crashes (i.e., a positive correlation between cannabis sales and less severe crashes). As indicated, although all these studies showed association, causality was not demonstrated.

Like those conducted in Washington State, pre/post RML studies conducted in Colorado also showed an increase in cannabis use among crashed drivers after legalization (Aydelotte et al., 2019; Aydelotte et al., 2017; Monfort, 2018), although some of these studies were based on the FARS, a database not recommended for drug-related analyses (Berning & Smither, 2014).

An important point was made recently by Manthey and colleagues (2023): Although there is no clear evidence that legalization has increased crash risk, no study has reported that legalization has reduced crash risk either.

An approach often used to estimate cannabis-related crash risk was also based on the FARS database (e.g. Bartos et al., 2020; Calvert & Erickson, 2020; Fowles & Loeb, 2021; Kamer et al., 2020; Pollini et al., 2015; Santaella-Tenorio et al., 2020). Unfortunately, as previously noted, the limitations for drug-related analyses using the FARS database hampers the validity of these studies, as well as of the reviews and meta-analyses that include them (Windle et al., 2022).

Using data from the National Center for Health Statistics' Division of Vital Statistics, Marinello and Powell (2023) recently conducted a difference-in-differences analysis to estimate the impact of RML on overall fatalities from motor vehicle crashes, and estimated that recreational markets were associated with an overall 10% increase in motor vehicle crash deaths.

Responsibility and culpability analyses were also used to examine DUI-C. Recently, Brubacher and colleagues (2023) used a sample of non-fatally injured motor vehicle drivers in British Columbia, Canada, found no evidence of increased crash risk in drivers with THC < 5 ng/ml in blood, and a statistically non-significant increased risk of crash responsibility (odds ratio = 1.74) in drivers with THC $\geq$ 5 ng/ml.

Using hospital data from Argentina, a recent study by Conde and colleagues (2023) reported that alcohol use alone as well as combined alcohol and cannabis use significantly increased crash risk. This study also measured association, but not necessarily causality.

A literature review conducted by White and Burns (2023) and a meta-analysis conducted by the same authors (2021) concluded that the risks from driving after using cannabis are lower than from drink-driving, speeding, or using mobile phones while driving.

Other Injuries. The 2017 NASEM review concluded that "There is insufficient evidence to support or refute a statistical association between general, nonmedical cannabis use and occupational accidents or injuries" (NASEM, 2017). Current reviews have reached similar conclusions. In their review, Allaf and colleagues (2023) found that although most studies reported an association between RML and an overall increase in the incidence of cannabis poisoning, the authors argued that the probable cause for such an increase was the increase in cannabis availability, access, and use after RML. Also in a recent review, Walker and colleagues (2023) indicated that most studies reported an increase in cannabis-related ED visits after RML; however, the authors acknowledged that many of the included outcomes had "serious risk of bias due to failure to control for many important confounding domains."

Nevertheless, although no significant overall change in poisoning rates was detected, it has been suggested that the risk of overdose injuries, including respiratory distress and non-intentional

poisoning among children may have increased (NASEM, 2017; Allaf et al., 2023). More research into this possibility is needed.

Other Health-Related Outcomes

Allergies. Allergic reactions to cannabis use can present with symptoms of rhinitis, conjunctivitis, asthma, or cutaneous reactions (relating to or affecting the skin) (Skypala et al., 2022). Research on this topic is still in its infancy (Toscano et al., 2023).

Cannabis Hyperemesis[11] Syndrome. First reported in 2004, cannabis hyperemesis syndrome is a form of functional gut–brain axis disorder characterized by bouts of episodic nausea and vomiting worsened by cannabis intake (Perisetti et al., 2020). Cannabis cessation is reported to be the most successful management of symptoms, although the syndrome may recur if cannabis use restarts (Hall & Lynskey, 2020; Senderovich et al., 2022). Only a small number of deaths have been attributed to this syndrome (Hall & Lynskey, 2020).

Prenatal, Perinatal, and Postnatal Exposure to Cannabis. The 2017 NASEM review reported that although there is no evidence of an association between maternal cannabis smoking and pregnancy complications for the mother, there is substantial evidence that maternal cannabis smoking is associated with lower birth weight of the offspring (NASEM, 2017). Cannabis use during pregnancy has also been associated with a dose-dependent decrease in fetal growth, adverse neonatal outcomes, and neonatal intensive care admissions for increased respiratory and neurologic infections (Marchand et al., 2022).

The association between maternal cannabis smoking and later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) is less clear (NASEM, 2017). Recent research has suggested that prenatal exposure to cannabis may interfere with normal development and maturation of the brain, which could cause children who have been exposed to cannabis in utero to show impaired attention, learning, and memory, as well as impulsivity and behavioral problems (Riggs & Thant, 2022; Brown et al., 2021). Further, recent research has provided some evidence that prenatal THC exposure can alter placental and fetal DNA methylation at genes involved in neurobehavioral development, a change that may have a long-term impact on child outcomes; however, this association has not yet been demonstrated. (Shorey-Kendrick et al., 2023).

Oral Health (Periodontitis[12]). Because tobacco smoke is a well-known risk factor for periodontitis, studies have examined the biological plausibility for a possible relationship between periodontal disease and cannabis use (Chisini et al., 2019; Mayol et al., 2021; Scott et al., 2022).

There is consensus that smoking cannabis is associated with a higher prevalence of periodontitis. The association between cannabis use and periodontal disease occurs independently of the use of tobacco, although a synergic effect may be observed, leading to a higher prevalence of periodontitis among individuals that use both drugs (Chisini et al., 2019; Scott et al., 2022).

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[11] Hyperemesis refers to severe abdominal pain and cyclical vomiting.

[12] Periodontitis is a serious infection of the gums caused by bacteria that have been allowed to accumulate on the teeth and gums.

In their review, Mayol and colleagues (2021) added that the detrimental impact of cannabis smoke on periodontal tissues was higher among frequent cannabis smokers and could be dose-dependent.

Kidney Functions. A recent study based on a nationally representative sample of U.S. veterans reported no significant association between cannabis use and acute kidney diseases (Potukuchi et al., 2023). Another recent study by Rein and colleagues reported that cannabis consumption did not adversely affect the kidney function of individuals without chronic kidney disease either. Both studies warned that these results need to be confirmed and the biological mechanisms fully understood, and they noted the need for additional research.

Cannabis and Male Sexual Behavior (MSB). The literature related to the effects of cannabis on MSB is scarce. Past animal research reviewed by Rodríguez-Manzo and Canseco-Alba (2023) showed that the pharmacological activation of CB1 and CB2 receptors with a mixture of cannabinoids was associated with a dose-dependent inhibition of MSB. The causality of this association has however been challenged, as it was argued that the reduction in MSB could have been caused by the sedation effect of the cannabis doses used in those studies (Mondino et al., 2019).

Rodríguez-Manzo and Canseco-Alba (2023) also reviewed the scarce literature as it applies to humans, and reported that cannabis consumption seems to have a bidirectional effect on sexual activity: low, acute doses may enhance human sexual functioning, specifically increasing sexual desire and satisfaction in some subjects, while large doses may produce negative effects on sexual functioning such as a lack of interest in sexual activity, erectile dysfunction, inhibited orgasm, and affecting sexual motivation. The authors nevertheless warned that there were several studies that either did not find any effects of cannabis on MSB or reported contradictory results. The authors argued that the different outcomes in those papers might be related to the multifactorial nature of human sexual behavior in the interpretation of the self-perceived sexual effects of cannabis use.

Cannabis and Emergency Department (ED) Visits. There is consensus that cannabis-related visits to EDs are not as frequent as alcohol-related ED visits (Crocker et al., 2023). Earlier administrative reports (up to 2016) reported statistically significant increases in the number of ED visits for cannabis-related events for each year examined (Shelton et al., 2020),

Recent reviews report an increase in cannabis involvement in ED visits in the U.S. over time, particularly for traffic-related injuries in jurisdictions with a prevalence of cannabis with higher THC content (Roehler et al., 2022; Crocker et al., 2023); however, it is unclear whether the increase in ED visits is associated with causality (cannabis impairment) or prevalence (an increase in cannabis use by the population) (Myran et al., 2023).

A recent study conducted in Canada shows an increase in cannabis-related ED visits in Ontario in past years, which has recently flattened even in the face of cannabis legalization and deregulation of retailers/edibles (Kim et al., 2022).

Cannabis and COVID-19 Outcomes. A 2020 NHTSA report authored by Thomas and colleagues (2020) indicated that drug prevalence among seriously or fatally injured drivers was high before the COVID-19 public health emergency began and even increased during the pandemic, especially for alcohol, cannabis (THC), and opioids. The study pointed out that during the COVID pandemic, THC was more prevalent among the seriously or fatally injured drivers than alcohol. The

authors made the point that their results showed the impact of COVID-19 on prevalence, but not necessarily on driver impairment (i.e., whether the drugs were impairing at the time of the crash).

Recently, Bonnet and colleagues (2023) reviewed the scarce literature on the impact the use of cannabis may have had on COVID-19 outcomes. The authors reported that although the use of cannabis did not impact mild COVID-19 symptoms, individuals who used cannabis experienced more COVID-19–related hospitalizations; however, they pointed out that the validity of these studies was questionable, as they were based on a very limited number of studies, which made causality difficult to assess.

Research also showed that the SARS-CoV-2 virus can cause excessive immune response and trigger an inflammatory cascade in the body. Because cannabinoids have been found to regulate these processes, researchers were interested in whether cannabis could play a role in the treatment of COVID-19 (Preteroti et al., 2023). Research on this topic was scarce, and harmed by methodological problems (Janecki et al., 2022). There is little evidence (a single study) showing that individual use of cannabis during the pandemic increased, decreased, or stayed the same, depending on relevant risk factors (e.g., access, dependence) (Harrell et al., 2022).

Therapeutic Use of Cannabis

Although the potential and/or actual therapeutic use of cannabis has been briefly discussed in previous sections, this section reviews topics that have not been discussed in previous sections associated with the therapeutic use of cannabis.

The most common self-reported therapeutical reasons for using cannabis include the treatment of pain, as well as for addressing mental health and sleep problems (Maddison et al., 2022).

In their 2022 review, Klein and Clark (2022) pointed to a lack of high-quality clinical trials on the therapeutic use of cannabis, but noted that certain dosage forms (e.g., tablets, capsules, injectable) and routes of administration seem to have a favorable impact on risk–benefit ratios for epilepsy and chronic non-cancer pain.

Concerns about the interaction between cannabinoids and medical drugs have been raised, including the possibility of adverse drug events that could emerge when cannabis use is paired with medications that treat HIV/AIDS, or with stimulants like cocaine (Brown et al., 2021).

A number of medical conditions and associated symptoms have been approved by state legislatures as qualifying conditions for medicinal cannabis use, in particular, for relief from the symptoms of cancer, glaucoma, HIV/AIDS, and multiple sclerosis (Bridgeman & Abazia, 2017).

The Food and Drug Administration has approved one plant-based marijuana drug and two medications made from synthetic chemicals that mimic the actions and effects of THC, which are only available with a prescription from a licensed healthcare provider:

- Epidiolex contains purified CBD from the marijuana plant. The drug is approved for treating seizures associated with two rare and severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome), as well as seizures associated with a rare genetic disorder (tuberous sclerosis complex) (Breivogel & Pulgar, 2023; Kluemper, 2022; National Institutes of Health, 2019).

- Dronabinol (brand names: Marinol and Syndros) and nabilone (brand name: Cesamet) are made from lab-created chemicals that act like THC by turning on cannabis receptors in the brain. These two medications are used to treat nausea in patients with cancer who are undergoing chemotherapy treatment and to increase appetite in individuals with AIDS who do not feel like eating (wasting syndrome) (Breivogel & Pulgar, 2023; Kluemper, 2022; National Institutes of Health, 2019).

Pain Relief. The most frequently reported use of medical marijuana is for pain relief. The 2017 NASEM report concluded that there was conclusive or substantial evidence that cannabis is effective for the treatment of chronic pain in adults (NASEM, 2017). Recent reviews compared the use of cannabis versus placebo and concluded that the effect sizes of the pain-relief use of cannabis were of questionable importance, with some research showing cannabinoids having no effects on acute pain or cancer pain while increasing the risks of non-serious adverse events (Barakji et al., 2023; Bialas et al., 2022). Also, the usefulness of CBD as a pain reliever may vary depending on the type of injury and the intensity of the pain (Thomas, Carter et al., 2022). Despite these recent concerns, a review of the literature by Soliman and colleagues (2021) concluded that the evidence supports the potential of cannabinoids to induce analgesia (pain relief).

Despite the lack of definitive scientific evidence, cannabinoids are already regularly used for the treatment of pain in diseases and conditions for which no other therapy options are effective or not well tolerated (Hidding et al., 2023); however, it has been pointed out that because more research is needed, the therapeutic use of cannabis should still be conducted with caution, as THC may cause significant side effects (Eeswara et al., 2023).

Nausea and Vomiting. In 2017, the NASEM report concluded that there was conclusive or substantial evidence that oral cannabinoids can be used in the treatment of chemotherapy-induced nausea and vomiting (NASEM, 2017).

Some pregnant women are increasingly treating nausea symptoms with whole cannabis or CBD alone (Volkow et al., 2019); however, the specific impact of fetal CBD exposure on negative outcomes is unclear. As indicated, studies conducted in animal models have shown that cannabis exposure may be associated with adverse embryonic development and postnatal outcomes (Brown et al., 2021; Swenson et al., 2023; Sandini et al., 2023).

Clinical Antitumor Effects of Cannabinoids. Although the clinical approval of cannabinoids is largely restricted to palliative uses in various diseases, the antitumor effects of cannabinoids are beginning to be clinically assessed (Velasco et al., 2016; Aziz et al., 2023; Silva-Reis et al., 2023; Buchtova et al., 2023; Erukainure et al., 2023; Akinloye et al., 2023). The review of the literature conducted by NASEM in 2017 had already suggested cannabinoids may have an antitumor effect; however, under certain conditions, cannabinoid treatment may stimulate cancer cell proliferation *in vitro* and interfere with cannabinoids' tumor-suppressor role (Velasco et al., 2016). Further, recent research has also suggested that cannabidiol and cannabis extracts may effectively counteract the anticancer effects of widely used standard-of-care drugs (Buchtova et al., 2023).

Despite the need of clarity, current research is searching for cannabis-based compounds to effectively induce cancer cell death (e.g. (Blal et al., 2023; Dada et al., 2023; Freire et al., 2023), as well as for mechanisms to effectively deliver cannabinoid-based medicines to work against cancer (Kaur et al., 2023; Freire et al., 2023; Buchtova et al., 2023).

Glaucoma. Cannabis has also been suggested for the treatment of glaucoma due to the potential for cannabis to alleviate intraocular pressure and have neuroprotective effects (Järvinen et al., 2002). In 2017, the NASEM report indicated that the beneficial effects of cannabis to treat glaucoma can be offset by ophthalmic side effects, and the fact that the effects of cannabinoids on intraocular pressure do not last long (NASEM, 2017). More recent reviews of the literature indicate that research on this issue is still needed (Wang and Danesh-Meyer, 2021; Passani et al., 2020).

Sleep Disorders. As recently reviewed by Maddison and colleagues (2022), about 50% of the U.S. population reports lack of adequate regular sleep. It has been posited that CBD, because of its action within the endocannabinoid system and the activation of CB1 and CB2 receptors, has the potential to be used to restore normal sleep (Gendy et al., 2023; Maddison et al., 2022). The 2017 NASEM report indicated that there was moderate evidence that cannabinoids were effective in improving short-term sleep outcomes (NASEM, 2017).

Research on the potential use of cannabis to treat sleep disorders has been clouded by methodological problems, such as the lack of adequate controls, unclear identification of CBD concentrations, and reliance on self-report measures of sleep quantity and quality (Maddison et al., 2022).

Recently, Bidwell and colleagues (2023) reported that naturalistic use of cannabis was associated with better sleep quality, particularly for those using edible and CBD-dominant products. H; however, another recent review by Amaral and colleagues (2023) reported inconsistent results. The authors concluded there is a "lack of robust evidence to support the use of cannabis for sleep disorders" but acknowledged that methodological issues may have clouded the research. They concluded that there is currently no robust evidence to support the use of cannabis for sleep disorders, and that more research is needed (Amaral et al., 2023; Luchowska et al., 2023).

CBD as a Treatment for Psychosis. CBD, which has a different mechanism of action than other antipsychotic medications, has been suggested as a novel treatment for psychosis, particularly during the early phases of the disorder. It has been posited that CBD could be especially helpful in patients who do not respond to treatment with antipsychotic medications and in patients who are reluctant to take antipsychotics because of concerns about side-effects and stigma. The 2017 NASEM report concluded that there was no or insufficient evidence to support the use of CBD to treat individuals with schizophrenia or schizophreniform psychosis (NASEM, 2017). A more recent review reports that research on this possibility is still lacking (Chesney et al., 2022).

Cannabis as a Tool to Slow Down Cognitive Aspects of the Aging Process. Research conducted in animal models indicates that physiological aging appears to occur in parallel with a decline in the expression and activity of CB1, suggesting that cannabis could be used to increase the CB1 activity, which may help slow down the physiological aging process (Zamberletti & Rubino, 2022). Research on this topic conducted in rodents using low and extremely low doses of THC has shown some promising results, but these early findings are highly inconclusive (Zamberletti & Rubino, 2022). The 2017 NASEM report included research conducted with hospitalized patients, but found no sound evidence that the use of cannabinoids was effective for the treatment of dementia (NASEM, 2017). The potential benefits of using CBD for improving the behavioral and psychological symptoms of dementia have generated increasing interest among researchers. The available evidence, however, is inconclusive (Leszko, 2023; Trojan et al., 2023).

Cannabis as a Harm Reduction Strategy for People Who Use Other Drugs. Research has suggested the possibility that cannabis could be used to reduce harm from some prescription drugs and/or substances, including alcohol, tobacco, and opioids (Lo et al., 2023; Charoenporn et al.,

2023). CBD has been suggested as a mechanism to reduce opioid consumption following a traumatic injury (Klein & Clark, 2022). There is some evidence to support the use of CBD to treat opioid use disorder (Reddon et al., 2023), in particular for reducing drug-induced craving and anxiety (Lo et al., 2023; Schneider-Smith et al., 2020); however, research on this possibility is lacking, largely due to legal and methodological limitations (Klein & Clark, 2022; Lo et al., 2023).

The evidence for using CBD in treating cocaine use disorders, and/or polydrug use disorders was even less clear than what has been shown for opioid use disorders (Lo et al., 2023). Research is needed to ascertain the impact of CBD dosing and administration regimens in real-world contexts (Lo et al., 2023).

Cannabis to Alleviate Respiratory Symptoms. Cannabis smoking causes acute bronchial dilation, depending on the dose of THC. Such an effect suggests the possibility of short-term respiratory benefits associated with cannabis use (NASEM, 2017; WHO, 2016).

Research Evaluations of the Impact of Cannabis Laws on Public Health

This section reviews evaluations conducted on the impact that MMLs and RMLs have had on public health in the U.S., Uruguay, Canada, and Thailand. These evaluations were not included in previous sections.

United States: MMLs. In a 2018 review of the literature, Sarvet and colleagues (2018), found that after the medical cannabis laws were passed, there was an increase in cannabis use and CUD among adults, but the authors did not find any association between medical cannabis laws and adolescent marijuana use.

A 2021 review found little evidence that MMLs had a significant impact on cocaine use (Sabia et al. 2021). The evidence was stronger for cannabis and prescription opioids behaving as substitutes, although the evidence weakened after 2010 as heroin and fentanyl became responsible for a large share of opioid-related deaths (Sabia et al., 2021). The authors also reported that medical cannabis and alcohol have been behaving as substitutes, with the enactment of MML leading to a reduction in alcohol consumption (Sabia et al., 2021).

United States: RMLs. Evidence shows that the passing of RMLs has increased regular cannabis use among adult users (Hall & Lynskey, 2020); however, studies conducted in different states have yielded mixed results, with some studies reporting increased past-month use after RML enactment and other studies finding decreased marijuana use (Cerdá et al., 2020; Athanassiou et al., 2023).

An analysis of the National Survey on Drug Use and Health database found a very small post-RML increase in risk for CUD among respondents aged 12 to 17 years; however, the study had limitations intrinsic to a self-report database and did not account for potential confounders such as participants' mental health or tobacco use (Cerdá et al., 2020; Zellers et al., 2023)

There is evidence that RML enactment was associated with fewer deaths involving prescription opioids (Sabia et al., 2021).

The adoption of an RML leads to a decline in marijuana-related arrests among both Black and White adults. In absolute terms, the decline was greater for Black adults, but this was entirely a

reflection of pre-treatment differentials in arrest rates between Blacks and Whites (Fone et al., 2023).

As discussed previously, the impact of RMLs on traffic safety is unclear (Sabia et al., 2021). The long-term consequences of RMLs are further unknown because they will depend on how supply-side regulations affect production and prices of marijuana (Smart and Doremus, 2023).

Hawley and colleagues (2020) found some evidence suggesting that RMLs may have an impact on those who use medical cannabis, including an increase in prevalence of use, problems accessing preferred products legally, higher cost, and difficulties using a legal access system.

Uruguay. In December 2013, Uruguay became the first country in the world to legalize the sale, cultivation, and distribution of recreational cannabis. The expressed motivation for legalization was to eliminate the illicit drug trade and its associated violence and public health–related harms; drug possession for personal use had already been decriminalized in Uruguay since 1974 (Laqueur et al., 2020).

Unlike the for-profit commercial models that had been adopted by Colorado and Washington, Uruguay's approach to legalization was non-commercial, in the sense that it is the government that controls all large-scale production, requires user registration, limits the weekly quantities that a user may purchase, and prohibits advertising in all its forms (Cerdá and Kilmer, 2017; Laqueur et al., 2020; Queirolo et al., 2023).

Studies examining the impact of RML enactment in Uruguay have not found an association between the change in legislation and changes in the prevalence of adolescent cannabis use (Rivera-Aguirre et al., 2022) or self-reported frequency of adolescent use (Laqueur et al., 2020).

A study looking at motor vehicle crashes found an association between the number of people who self-cultivate cannabis and the number of motor vehicle crash injuries (Kilmer et al., 2022). Nazif-Munoz and colleagues (2020) reported that RML passage in Uruguay was associated with an increase in fatal motor vehicle crashes; these studies, however, show association, not causality.

Canada. As reported by Hall & Lynskey (2020), "*In October 2018, Canada became the second nation to legalize the sale of cannabis to adults. The goals of legalization were to eliminate the illicit cannabis market and regulate the production and sale of cannabis to protect public health and minimize youth uptake.*"

As described by Hall and colleagues (2023), "*Legalization has been associated with increased adult hospital attendances for psychiatric distress and vomiting, unintentional ingestion of edible cannabis products by children and hospitalizations for cannabis use disorders in adults. There is conflicting evidence on whether cannabis-impaired driving has increased since legalization.*"

Some evidence suggests that the age of cannabis initiation has increased since the change in legislation in Canada, which brought an apparent increase in use among Canadians older than 25 years old. Results for individuals younger than 25 years old are mixed, with the majority of studies showing no pronounced increase in use (Rubin-Kahana et al., 2022). Also, recent studies showed that after legalization there was an overall decline in the percentage of users who acquired cannabis from the illegal market. Being a heavy user, young, having less than a high school diploma, and specific consumer preferences were associated with the likelihood that users would continue to buy cannabis from a dealer (Manthey et al., 2023).

As is the case with Uruguay, Canadian policy is still at an early stage of implementation, and although some evidence is emerging, it is still too early to evaluate its impact (Hall & Lynskey, 2020).

Thailand. The Thai government authorized the use of cannabis for medical purposes in 2019. Three years later, in June 2022, Thailand allowed individuals to grow and sell cannabis (Kalayasiri and Boonthae, 2023). Such a rapid legislative change is taking place amid a not-well-regulated market for cannabis, which generates lack of transparency regarding the quality of cannabis products (Lerksuthirat et al., 2023), including products associated with the tourism industry (Phucharoen et al., 2023).

Summary of Findings from the Literature

Cannabis Pharmacology

- **Cannabinoids act primarily through action on the ECS**, a network of chemical signals and cellular receptors that regulates functions such as learning, memory, emotional processes, sleep, pain control, and immune responses. Two receptors are particularly relevant to the metabolism of cannabis: CB1 and CB2. CB1 receptors are primarily in the brain, largely concentrated in regions involved in memory, emotional responses, cognition, motivation, and motor coordination. CB2 receptors are found primarily in the body where they play a role in the regulation of the immune system. They also act on the gastrointestinal tract, liver, heart, muscle, skin, and reproductive organs.
- The Cannabis sativa plant has more than 100 different cannabinoids, including THC and CBD. Of these**, THC is the main cannabinoid with psychoactive properties.** CBD does not produce acute intoxication, has been used to treat refractory epileptic syndromes in children, and may have anti-inflammatory, anxiolytic (anti-anxiety), and antipsychotic indications.
- Because of its interaction with the ECS, THC can have an impact on the development of the brain, producing structural changes in areas of the brain associated with cognition and behavior. These structural changes have been known to occur primarily among those with early onset of use (during adolescence) and that are heavier users; it is unclear whether these structural changes in the brain are associated with actual behavioral changes and/or other effects.
- Interest in CBD has recently increased; however, very little is known about the pharmacokinetics[13] and bioavailability[14] of CBD for different uses.
- Most research has focused on the interaction of THC and CBD with the CB receptors in the ECS. Recent research indicates that THC and CBD can also interact with other receptors activated by ECS. **Research suggests that non-CB receptors may play a key but understudied role in addictive behaviors. Research on this topic is needed.**
- The route by which cannabis is used can impact the onset, intensity, and the addictive potential and negative consequences associated with use. THC is rapidly transferred from lungs to blood during smoking, with **the effects of smoking cannabis reaching their maximum effect after 15 to 30 minutes and typically disappearing within 2 to 3.5 hours; however, the impact of inhaled cannabis on some driving tasks may last 5 hours or more, depending on the THC dose and other factors.**
- Cannabis vaping onset, peak effect, and duration are similar to those of smoking. Because vaporization tends to provide effects similar to smoking, but with a reduced exposure to the byproducts of combustion, it was suggested that compared with smoking cannabis, vaping may have some benefits; however, very little is known about long-term impact of vaporized cannabis to the respiratory system and the possibility of the downstream development of lung diseases.

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[13] Pharmacokinetics is the branch of pharmacology concerned with the movement of drugs within the body.

[14] Bioavailability is the proportion of a drug or other substance that enters the circulation when introduced into the body and so is able to have an active effect.

- Following oral ingestion, psychotropic effects manifest within 30 to 120 minutes, reach their maximum effect after 2 to 3 hours, and last for about 4 to 12 hours, depending on the dose.
- **Synthetic cannabinoids**, also called Synthetic Cannabinoid Receptor Agonists (SCRAs), are a constantly evolving set of compounds that have undergone several changes over time. Compared with THC, the majority of SCRAs are highly potent, binding with a ten to a hundred times higher affinity at the ECS receptor.
- The majority of cannabinoids are highly lipophilic compounds that rapidly distribute into the brain and adipose tissue. THC and CBD have a half-life (i.e., the time required for the concentration of the drug to reach half of its original value) that is biphasic; a rapidly increasing effect phase followed by a plateau. The initial phase distributes THC to highly vascularized tissues, such as the lungs, heart, brain, and liver. After being absorbed, cannabinoids distribute to less vascularized tissues (e.g., adipose tissue) where they accumulate and are subsequently released. The release of cannabinoids from adipose tissue can take place for weeks after consumption.

  After inhalation, THC enters the bloodstream quickly through the lungs, with the peak achieved within 6 to 10 minutes after inhalation. As a result, peak THC concentrations are lower after oral THC ingestion than smoked administration, but conversely 11-hydroxy-THC/THC ratios are higher after oral than smoked cannabis.

  After oral intake, THC goes to the liver where it is metabolized into 11-hydroxy-THC (psychoactive) and then into 11-COOH-THC (not psychoactive) or it is eliminated. Although 11-hydroxy-THC can be formed after consumption of THC from inhalation (vaping, smoking) as well as from oral use (by mouth, edible, under the tongue), levels of 11-hydroxy-THC are typically higher when eaten compared to inhalation. Cannabinoids and their metabolites eventually are eliminated in the urine and feces.
- Chronic users redistribute inactive metabolites from adipose tissue into blood and urine, which is the underlying reason for positive urine drug screens weeks after last use and prolonged half-lives of different compounds.
- **The combined use of cannabis and alcohol may result in greater psychoactive toxicity than either substance alone**. Heavy alcohol and cannabis use during adolescence can further contribute to small to moderate disruptions in brain structure and function**;** however, the underlying mechanisms behind this outcome remain unclear.
- Very little is known about the pharmacology of combined use of nicotine and cannabis. Although research suggests cannabis and tobacco could each be used to counter the effects of the other, much research is needed before any therapeutic recommendation can be formulated.

Cannabis Potential for Abuse

- Cannabis use can have acute (short-term) as well as chronic (long-term) effects on human health.
- Although there is wide inter-individual variation, acute cannabis intoxication has been associated with enhanced sensitivity to colors and/or music, altered perception of time, decrease in short-term memory, dry mouth, impaired perception, and impaired motor skills. Cannabis can also impair memory, attention, and psychomotor functions, although the most robust effects were reported for verbal learning and working memory.

- **The wide range of acute effects rarely includes a fatal outcome**. Although overall, the risk of death due to cannabis overdose is lower than the risk dying by opioid or stimulant overdoses, the risk of death due to cannabis overdose increases when it occurs conjointly with traumatic physical injury, or in individuals with cardiac pathologies.
- Daily consumption of cannabis (THC) can produce persistent, chronic impairments in memory and cognition, particularly when cannabis use begins in adolescence.
- **Progression to cannabis dependence is associated with factors such as intensive use of cannabis and early onset.** The risk of developing cannabis dependence is higher with high potency THC strains with a low CBD content, large amounts consumed, high frequency use (heavy, daily), and with starting use early in adolescence.
- It has also been posited that flavors in inhaled cannabis products may impact cannabis dependence, but the evidence is weak.
- Contributing to the progression to dependence are psychological and mental health factors such as low self-esteem, self-control, and coping skills. Cannabis dependence tends to occur more often among individuals who report any lifetime psychiatric, mood, anxiety, conduct, and/or personality disorder, as well as those with attention deficit hyperactivity disorder (ADHD).
- Frequent use of cannabis may lead to **tolerance** to the impairing effects of THC on cognition and psychomotor function.
- **Tolerance breaks** or "T-breaks" have been proposed as a strategy for managing cannabis use. Unlike quit attempts, T-breaks are generally done without the desire to quit, with the primary goal of reducing tolerance levels so that a smaller amount of cannabis would be needed to achieve the same high when cannabis use is resumed. There is a dearth of scientific research on the topic.
- **Polysubstance use is common among cannabis users**. Cannabis is the most used drug among those who use alcohol, with individuals with cannabis use disorders (CUD) often showing alcohol use disorders, opioid use disorders, and/or nicotine dependence.
- **When used together, cannabis and alcohol are associated with worse performances than when cannabis is used alone.** The simultaneous use of alcohol and cannabis had a larger negative impact on drivers' visual function, although driving performance was only significantly affected by the higher alcohol dose**.**
- Although polysubstance use is common among cannabis users, there is little evidence in support of an association between cannabis and other drugs' initiation and/or quantity used. Almost 50 years ago, cannabis was purported to be a **"gateway drug**" for alcohol, tobacco, and other illicit drugs. **Recent studies not only reject the gateway hypothesis but indicate that cannabis initiation rarely precedes the onset of tobacco and/or alcohol use.**
- Evidence shows that the reinforcing and/or rewarding effects of cannabis at lower doses varies by individual's sex, with **individuals assigned female at birth showing a more rapid escalation of problems than those assigned as males at birth.**
- One of the motivations for cannabis legalization was to reduce racial inequalities regarding the disproportionate incidence of arrests and convictions of minorities for cannabis-related charges. Although, arrests for cannabis-related offenses have declined since legalization, that may not be the case with convictions and incarcerations. **Overall, it is too early to assess the impact of legalization on racial/ethnic minorities**.

- Cannabis use among individuals ages 50+ has increased following its legalization, mainly due to a combination of medical and quasi-medical reasons. Although cannabis use may help individuals with medical problems (e.g., to assist with sleep, control pain, stimulate appetite), older users may be at a higher risk than younger individuals of some adverse health effects, such as car crashes, confusion, dizziness, falls, and delirium. As a result, the benefit/risk ratio cannabis poses for older users remains unclear.

Impact on Public Health

- **Cannabis has been linked to negative as well as positive health outcomes.** A particular characteristic of cannabis is the possibility that use of the drug could generate negative outcomes and/or have therapeutic value. THC and CBD are largely responsible for these effects, with THC usually associated with negative and CBD with neutral or beneficial outcomes. The latter has been an oversimplification, as there is evidence that either one of these cannabinoids can induce positive and negative symptoms.
- **Health outcomes coming from laboratory studies are rarely confirmed by epidemiological studies.** Laboratory studies have consistently linked cannabis use to several negative as well as favorable outcomes, but for the majority of these outcomes, epidemiologic studies have yet to confirm or reject the laboratory findings.

Negative Outcomes

- Cancer
    - Laboratory studies have found evidence for the association between cannabis use and precursors for several cancers, such as head and neck cancer and bladder cancer, but the research has lacked consistency. Even less clear is the laboratory-based evidence of an association between the use of cannabis and the incidence of brain cancer, breast cancer, colorectal cancer, or skin cancer; however, some evidence shows that the risk of skin cancer increases among HIV-infected cannabis users.
    - Confirmatory evidence for these associations is lacking. No definite association between cannabis use and most cancer outcomes has been found in epidemiologic studies. The confirmatory evidence coming from epidemiological studies is stronger (albeit moderately) for an association between cannabis use and testicular germ cell tumor. A reason for such a relatively high confidence in this association is the absence of potential confounders in the research.
- Respiratory Diseases
    - Similarities between the process of smoking cannabis and tobacco (i.e., both processes involve the inhalation of the active compounds along with toxic combustion products) raised concern for the acute impact of cannabis smoking on the development of diseases that have already been associated with tobacco use, such as airway inflammation, chronic bronchitis, or emphysema.
    - Although cannabis smokers tend to display symptoms linked with asthma and COPD, such as cough, sputum and wheezing, it is unclear whether cannabis smokers are at a higher risk of COPD than non-smokers of cannabis.
    - Cannabis smoking can affect the function of key immune cells participating in the lung's defense against infection, which has raised concern that cannabis smokers could be at an elevated risk of developing pneumonia, in particular when using cannabis products

containing impurities. Concern is particularly elevated among susceptible individuals such as those that are immune compromised by HIV or cancer chemotherapy; however, evidence that cannabis smoke alters susceptibility to respiratory infection is lacking.

- Symptoms such as dyspnea, cough, fever, constitutional symptoms, gastrointestinal upset, and hemoptysis have been linked to vaping users. The occurrence of these symptoms, which were termed Electronic cigarette, or vaping product use-associated lung injury (referred to as EVALI), has been linked with the liquid used in the vaporization process (the e-liquid), which typically contains ingredients such as psychoactive agents (e.g., nicotine, THC), solvents, and flavoring compounds, all of them having potential health risks (e.g., toxic/chemical induced lung injury) either alone or in combination, as well as with the presence of Vitamin E acetate (a thickening agent for THC), which is a major contributor to the EVALI risk; however, a clear understanding of EVALI risk is lacking. Research on this issue has been challenged by several confounders, in particular difficulties with the identification of the sources of THC (unregistered sources associated with an elevated risk of EVALI) and cannabis vaporization devices and products (different cannabis vaporization devices and products carry different levels of health risk).
- Based on the tobacco experience, there is concern that second-hand cannabis smoking may also have a negative impact on individuals' health, particularly on children. Unfortunately, research on the impact of second-hand smoking on individuals' health is lacking.

- Cardiovascular Diseases
  - Laboratory analyses have found evidence suggesting that cannabis may have a negative impact on the cardiovascular system. Cannabis (THC) use can produce rapid changes in cardiovascular function such as tachy- and brady-arrhythmias, as well as changes in vascular contractility.
  - Laboratory studies have also suggested that like second-hand tobacco use, second-hand cannabis smoking may have an impact on vascular endothelial function.
  - The effects of cannabis use on cardiovascular diseases are generally mild and not life-threatening. Early research suggested that harmful cardiovascular effects occurred only in people with pre-existing heart disease. More recent research however, reported on case studies showing that acute exposure to cannabis, even by young healthy people, may lead to myocardial infarction, stroke, and other severe cardiovascular events. These symptoms tend to appear largely among heavy daily cannabis smokers, being less pronounced among young individuals.
  - While laboratory analyses have found evidence suggesting that cannabis may have a negative impact on the cardiovascular system, reports based on large national databases as well as cohorts-based studies are showing conflicting results, largely due to methodological limitations.
- Mental Health
  - Research has consistently reported evidence of a decrease in performance on verbal learning and verbal memory during acute cannabis intoxication.
  - Evidence links early onset of cannabis use, as well as frequent use of cannabis, with the likelihood an individual would develop CUD, as well as the occurrence of mood disorders, personality disorders, depression, panic attacks, agoraphobia, PTSD, and/or anxiety; however, the direction of the use of cannabis and mental health disorders is unclear, with

opposite causal directions being possible (having a major depressive disorder increasing the risk of cannabis initiation, and vice versa).

- Although research on the impact of cannabis on depression is equivocal, cannabis use has been more often associated with an increased, rather than decreased risk of depression.
- Some researchers have suggested that the impact of cannabis on anxiety may vary by sub-type of anxiety disorder, being more associated with elevated incidence of social anxiety but not for other types of anxiety. Factors such as cannabis use history, cannabis potency, pre-disposition to an anxiety disorder, and consumers' ability to understand/measure/control the dose they use may all affect the extent to which individuals experience the acute effects of cannabis as being anxiogenic or anxiolytic.
- Despite some recent studies linking cannabis use with bipolar disorder, recent reviews reiterated the limited knowledge in this field, and the need for more systematic studies.

- Injuries
  - Overall, injuries due to cannabis use are rare, but can occur when cannabis is used alone or with other substances, the latter concern is particularly high involving motor vehicle crashes.
- Motor Vehicle Crashes
  - Laboratory studies, in particular studies using a driving simulator, have shown that acute cannabis intoxication can affect the psychomotor skills necessary for safe driving, with this impairment increasing at higher doses of cannabis.
  - In these studies, the simultaneous use of alcohol and cannabis show a larger negative impact on drivers' visual function, although driving performance was only significantly affected by the higher alcohol dose.
  - Epidemiological studies have clearly shown a sustained increase in the prevalence of THC use among U.S. drivers.
  - The issue remains whether the well-documented increase in cannabis prevalence detected among motor vehicle crashed drivers denotes causality, or merely reflects an increase in use by the population (i.e., cannabis is increasingly detected among crashed drivers not because the drug caused the crashes, but because more drivers were using it). Unlike laboratory studies, epidemiological studies are showing mixed results.
  - The European Integrated Project DRUID and NHTSA's Drug Crash Risk study were two large studies aimed to assess cannabis crash risk. Both studies suggested a relatively minor contribution of cannabis to crash risk (unless cannabis is consumed simultaneously with alcohol); however, the findings from these studies do not rule out the possibility that cannabis could generate elevated crash risk. These studies presented limitations, including a limited range of THC values obtained from participant drivers, which did not allow for a detailed estimation of crash risk under different THC concentrations (e.g., under moderate and/or elevated THC concentration)
  - Pre-post comparative analyses of the impact of marijuana legalization on crash risk also yielded mixed results. Some studies found an association between the passing of MMLs or RMLs and motor vehicle crashes, but causality was not clearly demonstrated. In any case, while there is no clear evidence that legalization has increased crash risk, no study has reported that legalization has reduced crash risk either.

- An often-used approach for the estimation of cannabis crash risk was based on the FARS database. Unfortunately, the limitations for drug-related analyses present in the FARS database hamper the validity of these studies, as well as of the reviews and meta-analyses that include the use of FARS data.

- Other Injuries
  - The 2017 NASEM review concluded that, "There is insufficient evidence to support or refute a statistical association between general, nonmedical cannabis use and occupational accidents or injuries." Recent reviews have reached a similar conclusion.
  - Although most recent studies reported an association between RMLs and an overall increase in the incidence of cannabis poisoning, this finding is not necessarily indicative of cannabis being a poisoning drug, but a consequence of the increase in cannabis availability, access, and use after RML passage.
  - Nevertheless, although no significant overall change in poisoning rates was detected, the increasing availability, diversity, and potency of cannabis products has elevated the drug's potential for accidental injuries and death, and the prevalence of overdose injuries, including respiratory distress and non-intentional poisoning among children, has increased.
- Allergies
  - Allergic reactions to cannabis use can present with symptoms of rhinitis, conjunctivitis, asthma, and cutaneous reactions; however, research on the association between cannabis use and allergies is still in its infancy.
- Cannabis Hyperemesis Syndrome
  - First reported in 2004, cannabis hyperemesis syndrome is a form of functional gut–brain axis disorder characterized by bouts of episodic nausea and vomiting worsened by cannabis intake. Research on cannabis hyperemesis syndrome is lacking.
- Prenatal, perinatal, and postnatal exposure to cannabis
  - No evidence has been found of an association between maternal cannabis smoking and pregnancy complications for the mother; however, there is substantial evidence that maternal cannabis smoking is associated with lower birth weight of the offspring.
  - Cannabis use during pregnancy has also been associated with dose-dependent adverse neonatal outcomes, and neonatal intensive care admissions for increased respiratory and neurologic infections.
  - The association between maternal cannabis smoking and later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) is less clear. Recent research has suggested that prenatal exposure to cannabis may interfere with normal development and maturation of the brain, a change that may have a long-term impact on outcomes for children; however, the association between these negative outcomes for children and maternal use of cannabis has not yet been demonstrated.
- Oral Health (Periodontitis)
  - There is consensus that smoking cannabis is associated with a higher prevalence of periodontitis, particularly among frequent cannabis smokers. The association could be dose dependent.

- Kidney functions
    - Research has started to examine whether cannabis use could affect acute as well as chronic kidney disease. No clear association has been detected yet. The research is in its infancy.
- Male Sexual Behavior
    - The scarce literature related to the effects of cannabis on MSB reports contradictory results. Several studies found no effect. Those that reported some effect appear to paint a bidirectional effect on sexual activity, indicating that low, acute doses may enhance human sexual functioning, specifically increasing sexual desire and satisfaction in some subjects, while large doses may produce negative effects on sexual functioning such as a lack of interest in sexual activity, erectile dysfunction, and inhibited orgasm, and affecting sexual motivation.
- Cannabis and Emergency Department visits
    - Recent reviews report an increase in cannabis involvement in ED visits in the U.S. over time, particularly for traffic-related injuries in jurisdictions with a prevalence of cannabis with higher THC content; however, it is unclear whether the increase in ED visits is associated with causality (cannabis impairment) or prevalence (an increase in cannabis use by the population).
- Cannabis and COVID-19 outcomes
    - Research shows that although the use of cannabis did not impact mild COVID-19 symptoms, individuals who used cannabis experienced more COVID-19–related hospitalizations; however, the limited number of studies in which these studies were based made causality difficult to assess.
    - Drug prevalence among seriously or fatally injured drivers increased during the pandemic, especially for alcohol, cannabis (THC), and opioids; however, these results show the impact of COVID-19 on prevalence, but not necessarily on driver impairment.

Therapeutic use of cannabis

There are several medical conditions and associated symptoms for which medicinal cannabis use has been approved, in particular those aimed to relieve the symptoms of cancer, glaucoma, HIV/AIDS, and multiple sclerosis.

The most common self-reported therapeutical reasons for using cannabis are to treat pain, mental health, and sleep problems.

- Pain relief
    - The most frequently reported use of medical marijuana is for pain relief.
    - The 2017 NASEM report concluded that there was conclusive evidence that cannabis was effective for the treatment of chronic pain in adults.
    - Recent reviews compared the use of cannabis vs. placebo and concluded that the effect sizes for the pain-relief use of cannabis were of questionable importance. Some research suggested that the usefulness of CBD as a pain reliever may vary depending on the type of injury and the intensity of the pain.
    - Despite these recent concerns, the evidence supports the potential of cannabinoids to induce analgesia.

- Despite the lack of definitive scientific evidence, cannabinoids are already regularly used for the treatment of pain in diseases and conditions for which no other therapy options are effective or are not well tolerated.

- Nausea and vomiting
  - The 2017 NASEM report concluded that there was conclusive evidence that oral cannabinoids can be used in the treatment of chemotherapy-induced nausea and vomiting; however, concerns about negative drug-drug interactions have been raised.
  - Some pregnant women are increasingly treating nausea symptoms with whole cannabis or CBD alone; however, the specific impact that fetal CBD exposure has on negative outcomes for the child is unclear.
- Clinical antitumor effects of cannabinoids
  - Besides some pro-tumorigenic activity, there is evidence that cannabis also has some anti-tumor properties. The latter suggests the possibility that cannabinoids can be used to treat some types of cancers (e.g., skin cancer).
  - Such a favorable potential should, however, be balanced against research showing that under certain conditions, cannabinoid treatment may stimulate cancer cell proliferation and interfere with cannabinoids' tumor-suppressor role, and that CBD and cannabis extracts may counteract the anticancer effects of widely used standard-of-care drugs.
  - Well-designed human studies investigating the efficacy and safety of using cannabinoids for treating cancers are still lacking and the evidence is limited.
- Glaucoma
  - Cannabis has also been suggested for the treatment of glaucoma due to cannabis's potential impact on intraocular pressure and its neuroprotective effects; however, ophthalmic side effects and the short duration of cannabinoids' effect on intraocular pressure raised questions on this possibility.
- Sleep Disorders
  - It has been posited that CBD, because of its action within the endocannabinoid system and the activation of CB1 and CB2 receptors, has the potential to be used to restore normal sleep. Indeed, alleviating sleep disturbance is one of the most cited reasons for the use of cannabinoids.
  - Research on the potential use of cannabis to treat sleep disorders has been clouded by methodological problems, such as the lack of adequate controls, unclear identification of CBD concentrations, and reliance on self-report measures of sleep quantity and quality. Currently, there is no definite evidence to support the use of cannabis for sleep disorders. More research is needed.
- CBD as a treatment for psychosis
  - It has been posited that CBD could be a novel treatment for schizophrenia, bipolar disorders, and psychosis in general, being especially helpful in patients who do not respond to treatment with antipsychotic medications and in patients who are reluctant to take antipsychotics because of concerns about side effects and stigma. Research on this possibility is still lacking.

- Cannabis and social functioning
    - Some limited evidence shows an association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles. Research on this issue is lacking.
- Cannabis as a tool to slow down cognitive aspects of the aging process.
    - Research conducted in animal models indicates that physiological aging appears to occur in parallel with a decline in the expression and activity of CB1, suggesting that cannabis could be used to increase the activity of CB1, which may help slow down the physiological aging process, as well as for improving the behavioral and psychological symptoms of dementia. The evidence, however, is inconclusive.
- Cannabis as a harm reduction strategy for people who use other drugs.
    - Research has suggested the possibility that cannabis could be used to reduce harm from some prescription drugs and/or substances including alcohol, tobacco, and opioids. There is some evidence in support of the use of CBD to treat opioid use disorder, in particular for reducing drug-induced craving and anxiety; however, the research on this possibility is lacking.
    - There is also some evidence for using CBD in treating cocaine use disorders, and/or polydrug use disorders, but the evidence is even less clear than what has been shown for opioid use disorders.
- Cannabis and COVID-19
    - Because cannabinoids have been found to regulate some of the symptoms associated with the SARS-CoV-2 virus, researchers were interested in whether cannabis could play a role in the treatment of COVID-19. Research on this topic is scarce.
- Cannabis to alleviate respiratory symptoms.
    - Cannabis smoking causes acute bronchial dilation, depending on the dose of THC. As such, there may be short-term respiratory benefits associated with cannabis use; however, these benefits can be reversed by the effects of long-term cannabis smoking. The clinical implications of these experimental findings are unclear, as studies have yielded inconsistent results, largely because of methodological limitations.

Part II: Expert Opinion on the Potential Impacts of Cannabis Rescheduling on Public Health and Traffic Safety

The U.S. Drug Enforcement Agency currently recognizes cannabis as a Schedule I controlled substance under the Controlled Substances Act of 1970. Schedule I substances are defined as "drugs with no currently accepted medical use and a high potential for abuse" (Drug Enforcement Agency, n.d.). Recently, the possibility of rescheduling cannabis—moving it out of Schedule I—has been discussed. Moreover, the U.S. Department of Justice has submitted a proposed regulation to reschedule marijuana, moving the drug from Schedule I to Schedule III. A press release issued by the Office of Public Affairs of the U.S. Department of Justice on May 16, 2024, states that: "*The Justice Department today announced that the Attorney General has submitted to the Federal Register a notice of proposed rulemaking initiating a formal rulemaking process to consider moving marijuana from a schedule I to schedule III drug under the Controlled Substances Act (CSA).*" (DOJ, 2024)

Discussions about the proposed rulemaking (a proposed rescheduling of cannabis) need to be appropriately informed about the impacts this policy change would have on eight factors established by the Controlled Substances Act:

1. The substance's actual or relative potential for abuse.
2. Scientific evidence of the substance's pharmacological effect, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. The substance's history and current pattern of abuse.
5. The scope, duration, and significance of abuse.
6. What, if any, risk there is to the public health.
7. The substance's psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled.

To inform the debate, this research team conducted a review of the scientific literature focusing on the impact that cannabis could have on the factors listed above (see Part I for Literature Review). This review of the literature was complemented by two focus groups of expert panelists to gather various viewpoints about future public health and traffic safety scenarios that may occur were the rescheduling of cannabis to be approved. The two focus group sessions, held in May 2024, provided in-depth feedback about the impact rescheduling of cannabis may have on public health in general and traffic safety in particular. This section describes the methodology applied to conducting the focus groups and the qualitative analysis of the data, and then presents the results.

Methods

Participants

The research team invited 30 expert-level participants to participate in a 90-minute virtual focus group. The invitees had expertise in multiple public health arenas that might be impacted by the rescheduling of marijuana on the federal level. Invitees included representatives or retirees from organizations and agencies that have an interest in the topics of marijuana use and related policy. Efforts to include a diverse participant pool to ensure a variety of perspectives were considered were made. Invitees were offered a $100 Amazon gift card as a small token of appreciation for participation in a focus group. Ultimately, fourteen participants were available for the focus group dates and interested in participating in this study. Two focus groups with seven participants in each session were conducted in May 2024 by Pacific Institute for Research and

Evaluation (PIRE) staff with input from the AAA Foundation for Traffic Safety (AAAFTS). The participants included current employees or retirees from advocacy groups, organizations, academia, and government agencies related to traffic safety, impaired driving, law enforcement, marijuana use and policy, and toxicology. Nine of the fourteen participants were female. Three of the fourteen participants were unable to accept the gift card token, as the acceptance of gifts related to their work is prohibited by their employers.

Protocol

The PIRE Institutional Review Board deemed this effort to be exempt from review because (a) participants were invited to discuss a topic related to their expertise in their field of work and not recruited as private individuals and (b) the information obtained in the focus groups was recorded in a way in which the identity of the participants cannot readily be ascertained, directly or through identifiers linked to the subjects. Participants gave permission to record the focus groups for qualitative coding purposes. They were told that their names and organizations would be redacted from the transcripts and that the summary of the focus groups would not attribute particular answers or opinions to individuals or their affiliations.

A Focus Group Guide (see Appendix A) was developed to create a structured set of open-ended questions that align to the study objectives and encourage the participants to share their ideas. The guide was organized in a logical sequence, starting with introductory questions to build rapport and progressing to more specific, in-depth questions that address cannabis rescheduling. The guide instructed panelists to discuss the impact that rescheduling cannabis would have on public health in general separately from the impact on traffic safety. Panelists were also instructed to focus on the impact of rescheduling, not legalization. The guide was pilot-tested with one traffic safety specialist (who met the criteria for being a participant but was not included in these analyses) and the questions and topics were found to be understandable.

An invitation email (see Appendix B) was sent to all potential participants, and it explained that the research team wanted to explore what effects the potential rescheduling of cannabis in the U.S. to a lower level might have on a variety of clinical and public health fields, including but not limited to traffic safety.

Analyses

The first step in the data analysis was to de-identify the focus group transcripts and clean them. A team member (a) went through the transcripts and changed speaker names to speaker numbers for people who were not part of the research team, and (b) listened to the transcripts and fixed numerous errors in the text that were a result of the automated transcription process. This included fixing missing or misinterpreted words, making continuous sentences out of phrases that had been broken up into multiple sentences due to pauses, and punctuating appropriately to improve the intelligibility of the transcript.

The two cleaned transcripts were then uploaded to Dedoose®, a cloud-based software program that allows for analysis among team members (SocioCultural Research Consultants, 2018). An interpretive grounded theory approach was applied for data analysis. Interpretive grounded theory involves a flexible, iterative process that prioritizes the co-construction of meaning between the researchers and participants (Charmaz, 2014). The process begins with open coding, where data is initially broken down and examined to identify significant concepts. A total of 65 codes were created when reviewing the data from the two focus groups. Codes were applied 400 times to 130 various excerpts (see Appendix C).

Figure 1 (Saldana, 2016) illustrates the analytical process. As the research team engaged with the data, codes were identified that captured concepts, while remaining open to the context and nuances presented by participants. These codes were then grouped into categories, which were developed through a continuous dialogue between the data and the researchers' interpretations. Constant comparison, which is a method central to interpretive grounded theory where categories emerge from the data, was used throughout the process to refine categories, ensuring that they accurately reflected the participants' feedback. Using axial coding, which focuses on developing and relating categories into conceptual understanding, the researchers connected categories and subcategories, exploring the relationships and patterns that emerged. Finally, selective coding followed, where the researchers identified the core category that integrates all other categories into a cohesive narrative. Theoretical themes were generated as the researchers constructed a theory that reflects both the data and their interpretive insights. Throughout the process, memo-writing helped document reflections, decisions, and evolving understandings, highlighting the interpretive nature of the analysis.

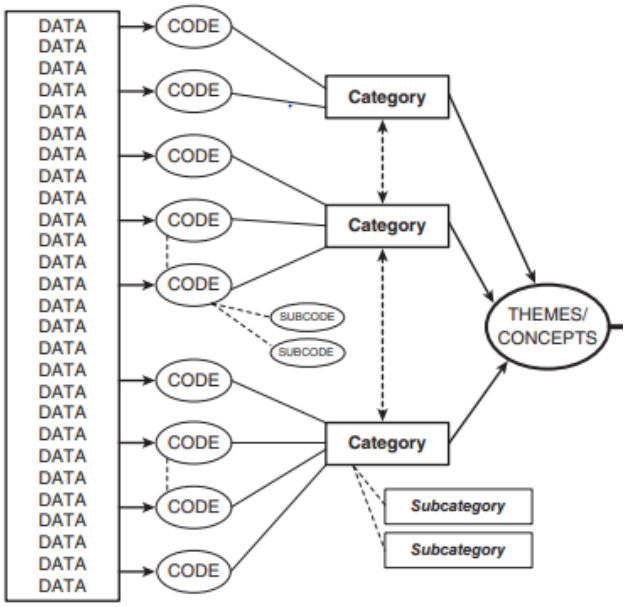

Figure 1: Grounded Theory: Analytical Process

Results

As indicated, the emergence of underlying themes in interpretive constructed grounded theory involves a detailed, iterative process where patterns and significant concepts are identified and refined. The transcript data was analyzed until thematic saturation was reached, where no new themes or categories emerged from the data. At this point, the identified themes are considered comprehensive and robust, and they represent what the experts' opinions on the rescheduling of cannabis means holistically. This section presents the results of these analyses.

Figure 2 depicts the four themes that emerged from the data, indicating the central findings of this grounded theory study: The experts believe that the main consideration of a potential cannabis rescheduling on public health or traffic safety would involve the dynamic relationship between perception and reality (i.e., how the public perceives what cannabis rescheduling on the federal level would mean).

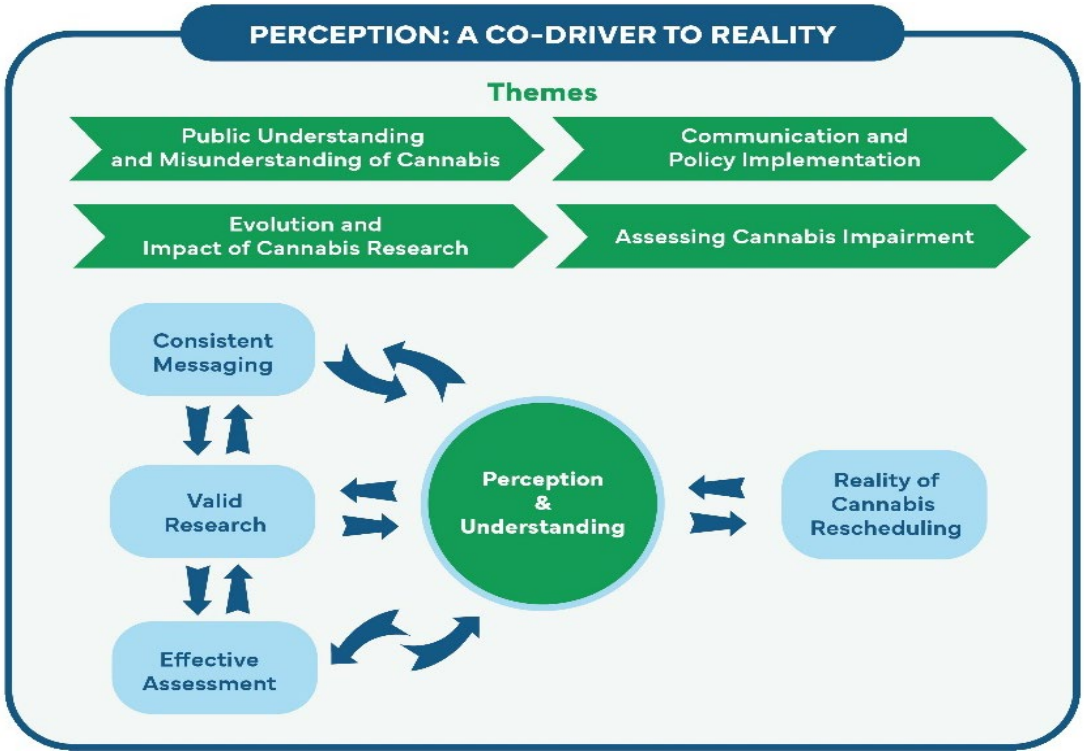

Figure 2. Themes and Core Categories

Theme 1: Public Understanding and Misunderstanding of Cannabis

Public perception is heavily influenced by understanding of the pros and cons of cannabis use and by existing misconceptions on the topic. This is a category with multiple subsumed codes that represent this theme.

This category effectively captures the essence of the various misunderstandings and confusions surrounding cannabis use, dosing, potency, different types, poly-use, potential harms, and the legal/rescheduling processes. Specifically, this category subsumes the following codes (Appendix C describes and defines each code) drawn directly from the two focus groups' data, and were noted 103 times, collectively:

- Rescheduling Process
- Decline in Perception of Harm
- Misunderstanding of Cannabis
- Drug Potency Impacts
- Cannabis Types
- Polydrug Use
- Cannabis Dosing

The two most prolific codes from this group (i.e., codes that most often surfaced in analyzing participants' opinions) were the Rescheduling Process (n=15) and Misunderstanding of Cannabis (n= 21).

The comments categorized in Rescheduling Process indicated that cannabis rescheduling to a lower category and possible federal legalization at some point are likely to occur; a multi-step process exists for rescheduling, there are steps to be taken, and proactivity in understanding that process is instrumental to being able to protect the public. At times, participants spoke of rescheduling in the context of full legalization of marijuana, anticipating a trajectory that a federal-level legalization could be in our future. Participants spoke of a lack of understanding about the process, asked questions about what next steps might include, and offered proactive suggestions that could occur. The following quotes from focus group participants exemplify these ideas:

"I think it's more likely to happen than not to happen, but certainly this is a process."

"The process is ongoing. There are a number of steps that remain in this process that could involve things like the DEA granting administrative law hearings and calling for additional evidence to be brought forward."

"There's different sets of expectations and you know immediately when they announce the rescheduling there were law enforcement agencies and,…they were being besieged by politicians and the community about when's it gonna make it legal."

"It may be no really discernible short-term effect, but I do think the rescheduling could have a long-term effect…"

"So I think it's important to have these discussions [about cannabis rescheduling] proactively beforehand…so we're not sort of caught with our pants down."

"…You need to get in front of it and right now no one really is."

"I think one of them is as we kind of go directly back to the question about the change in classification, the one thing that that pops up there in my mind, from an unintended consequences [standpoint], what happens for federally regulated jobs? We talked earlier about, you drive for a living. You know what is the implication? If it's now a Schedule III and somebody has got a prescription at the state level for using it right now, you can't operate a bus or train or airplane or truck what based on federal law. But what are the implications of that for a federal level? I don't know if NHTSA has looked at [that]. What would happen from that perspective if it's rescheduled, then all of a sudden you know you could get somebody that goes to court and you know well, can you regulate what somebody does off duty for a drug that's now no longer a Schedule I drug?"

"I think there's a lot of uncertainty, at least for me in terms of, you know, what does this rescheduling look like and what are the implications down the stream?"

Another prevalent code that emerged in these data was Misunderstanding of Cannabis. This code was applied when a participant referred to public perception that might be incorrect or limited in some way about cannabis (potency, dosing, impact on cognition, poly use with other drugs, law/policy, etc.). The following quotes illustrate this code:

"We're figuring it out, but the fact that we don't know what cannabis to move to Schedule 3… I don't know what that's gonna look like, is a big concern… I guess that

the lay person may not even know the rescheduling's happening or may not have a big effect on them."

"I also think it will, and it feels like there will be minimal change after rescheduling, just purely on an understanding and education point of view. The term rescheduling, you can't instinctively know what that means immediately. So for the lay person it's like, what does that mean? Legalization—It's got the word legal in it. It's probably easier to understand, but the amount of conversations I've had with people that don't understand what decriminalization is, that is also potentially not a quick thing to understand. So I feel as again if I don't understand what rescheduling is, it probably won't make any difference to my day-to-day because can I buy it legally now?"

"One of the [misperceptions of cannabis use] that emerged very early in our state is I'm going to smoke a little weed to sober up and then drive home."

"When you talk to young people, the big thing is a couple of drinks, a couple of beers, and a couple of joints. I mean, and they don't realize how they interact, and how a couple of beers in a night might not hurt you, a couple of joints I think would, but that's what it is, it's alcohol and cannabis together in the young people and they don't realize how dangerous that can be."

"I think a lot of people don't really understand what rescheduling means, and I think that can also play a huge role in perceptions and later behaviors."

Theme 2: Communication and Policy Implementation

Effective and coordinated messaging is crucial to align public perception with regulatory intentions and to ensure trust in the legal framework. As noted by the experts, current misalignment in communications and implementation is cause for concern on the future roll out as depicted in the Misalignment in Communications & Implementation category that emerged from these data.

This category captures the lack of alignment in messaging, coordination, information sharing, and application/implementation of policy/law with regards to cannabis use. The category includes the following codes (see Appendix C for further detail), which were noted 80 times in the data across the two focus groups:

- Distinction from Alcohol Impairment
- Medical Doctor Comfort with Cannabis Knowledge & Information Sharing
- Lack of Prosecution Follow Through
- Messaging
    - Coordination of Messaging/Roll Out
    - Negative Perception of Messaging
- Role of Federal Government
    - Institutional Mistrust
- State Testing and Regulation

- Strengthening Adjudication System

Messaging and the codes subsumed within messaging were the most prevalent of this category (n=33). Participants spoke to the importance of how we communicate rescheduling and any other policy/law associated with cannabis. How the message is rolled out, and the accuracy of the message, were noted as particularly relevant to public health and traffic safety outcomes. A lack of trust is suggested in some of the language that participants used. The following quotes magnify this:

> *"...the real problem I have with the way this was laid out in terms of restructuring or relabeling or reclassifying marijuana is it doesn't seem to me like it was well thought out in terms of how you're gonna message this issue."*
>
> *"…if you're going to do this, I certainly hope it's not because of politics. Because if we're doing it now because [it's] an election year and it's because of politics, it's the wrong approach. It's not good for the community. It's not good for understanding the issue and last but not least, it's not good for public health, nor the traffic safety issue."*
>
> *"And so messaging what rescheduling means, not just in the medical community, but also in the other communities affected by this issue is incredibly important."*
>
> *"The fact that the federal government for 50 years [said] that marijuana is in the same category as heroin now it says it's in the same category as ketamine. I think most Americans are going to disregard either message because they're going to say I don't think those messages make sense."*
>
> *"…a quick note about messaging, how important messaging is and the misinformation. The great example of like sativa versus indica, there is so much misinformation about sativa will give me, you know focused and energized and there's not a scientific basis for those two types of classifications. And I think that kind of drives the point that we need more education and messaging to help people make informed decisions about their use."*
>
> *"…from the medical piece and everything else, the whole understanding of what rescheduling means is not very well understood by most people and by the public."*
>
> *"When it comes to getting information from the federal government around cannabis, they're not the most credible source and our young people know that."*

Theme 3: Evolution and Impact of Cannabis Research

Continued cannabis research is vital to inform policy and public understanding, highlighting the need for adequate funding and resources. As noted below in the Research Exploration category, some of the experts noted the drawbacks in current restrictions related to cannabis research, they see potential value in advancing cannabis research, and they note improved research opportunities as one of the pros related to the impact rescheduling could have on both traffic and public health safety.

This category conveys the dynamic and forward-looking nature of several references to existing empirical evidence, covering past, present, and future research activities. It also aligns with quotes around funding and resourcing to continue our understanding of how cannabis impacts

public health and traffic safety. This category emerged 27 times and included the following codes (see Appendix C for further detail):

- Improved Research Opportunities as an Outcome of Rescheduling
- Challenging Existing Research
- Citing Research to Support Perspective
- Funding/Resourcing for Research

Improved research opportunities are seen as beneficial and perhaps a positive outcome of rescheduling cannabis. Participants spoke to existing research, often with reservations or critiques on limitations. Participants advocated for more research, and expressed the belief that more resources and funding for future research may emerge as a result of cannabis rescheduling.

> *"…can't do the research and now you will be able to…"*
>
> *"…we are excited about the idea that research could be easier to do…."*
>
> *"As far as testing and actually doing research on cannabis, there are [a] multitude of research centers across the country. They're doing dosing studies, have been doing it for decades. One well-known researcher, [name withheld], she's a psychobiologist. She's been studying this stuff for like over 50 years. And cannabis in particular... It's astounding. She has some really just fantastic insights of doing this research for 50 years. And people can do the research. You know, you don't need all this kind of, you know, some of these legislation pieces to be kind of unveiled for people to do the research. It may be harder to get the paperwork and get it done. It's being done. My buddy here, Speaker 4, and his group has been doing it for you know, a long time. So and there are many, many other people across the country."*
>
> *"…So, on the question of whether or not rescheduling itself would increase traffic safety problems, I see no reason to believe that would be the case. I'm gonna drop in the chat a link to some summaries, abstracts of studies that NORML compiled. As was mentioned, I think there is no evidence that medical cannabis laws are associated with increases in traffic fatalities."*
>
> *"I think with Schedule III, research on how to better understand and how to control for quality, control for dosing, control for method, can be better addressed with research again not for non-medical purposes or recreational legalization, but from moving from Schedule I to Schedule III."*
>
> *"NHTSA's been trying really hard to do that study again (drug crash risk case control study)…And you know, there was all the problems about the NHTSA surveys and things like that. That slowed things up. What was really interesting about that study, it was all set to go in Baltimore and at the very last minute, the Baltimore political thing said, no, we don't want it. So they moved it to Virginia Beach. It was one location. Almost all NHTSA's stuff is multiple locations and it was meant to be crashes. Impactful crashes and it ended up… and if you read if you read everything NHTSA's put out about it, it's quite understandable. Virginia Beach is a huge military establishment. They've got ships, planes, you know, just everything. So the militaries test all the time for drugs, right? They, you know, they do random testing at any point. So drug use in the community was quite down. That was one of the problems they ended up primarily*

with fender benders. Not serious crashes, injuries, deaths. Whatever. So it wasn't the population that they were looking for either. If you also go to the DRUID [Driving Under the Influence of Drugs, Alcohol and Medicines] study that was run in 13 countries in Europe, uh, they ended up once they adjusted for sex and age the odds ratio for cannabis went down to non-significant. But if you looked at the statistic of responsibility for a fatal crash, it was over two."

"That's even more murky in the research, and even though I agree there is a lot of cannabis research, there's still a lot of disagreement around traffic safety. Within that research about the effect that THC, especially by itself, especially if we're using crash data, because it's hardly ever by itself in the crash data, and just like the trauma study that was just done, looking at substances in crashes, I think at least in our state we have a per se for alcohol and we have a per se for THC."

"So my two things I agree about the research. You can do it now. I mean, I've been doing it for a very long period of time. It's a pain in the neck. It takes time. It takes work whatever, but you can. You can do the studies, so going to three is not going to change much. I'm disappointed because I know the DEA has approved other laboratories besides the one in Mississippi to supply other forms of cannabis, but I myself don't know of anybody who is actually doing that yet."

"I do still think yes, there's a ton of research that's going on around this. I do a lot of it as well, but there's so much more we need to do. I mean, I OK if it doesn't allow us to actually look at real world products, that's a huge problem and will continue to be a big one until we can do that because right now people are terrible at reporting the amount of potency that's in their actual products."

"I would argue that the biggest impediment we have right now when it comes to real world research is if you live in California, where cannabis has been legal medicinally since 1996 and it's been legal for adult use for the better part of more than the last half decade. If you live in San Francisco and say you work as a doctor at UC San Francisco and you want to do a study on the real-world products, San Franciscans are buying at retailers. You can't do that study because you're not permitted to use cannabis that's sourced from state legal sources. It has to come from a federally approved source; that my understanding is not going to change if cannabis moves to Schedule III. So if we don't move, that doesn't allow us to do the clinical work we wanna do and it doesn't allow us to test the product we say we want to know more about. So again, I don't see… on the margins, it may have some influence. Maybe they'll be more money allocated toward doing studies."

"Obviously there is a boatload of research that is being done and has been done about cannabis and your introduction, and you talk about the ABCD study, which is a longitudinal study looking at the development of young people who have been exposed to cannabis and those who haven't. That study is happening right now."

Theme 4: Assessing Cannabis Impairment

Reliable assessment methods are essential to maintain public confidence in safety measures and address the unique challenges posed by cannabis impairment. They are also seen as necessary to promote a consistent and reliable adjudication system for traffic offenses related to cannabis

impairment. While the other themes and categories presented were shared in discussions about public health and traffic safety outcomes, this theme was unique to traffic safety.

Participants made 44 references to how we currently assess cannabis impairment, how we could assess cannabis impairment, and how it differs from all other drug and alcohol assessments. Participants spoke to roadside assessment of cannabis impairment and their current confidence in measurement practices. This includes the tools (both behavioral and biological) used to assess impairment, as well as the training that law enforcement receives. Codes included the following:

- Assessment Tools/Techniques
- Toxicology Assessment
- Assessing Impairment Training

The following quotes speak to the importance of the integration of tools, toxicology, and training for assessing driving impairment. Specifically, the combination of using video cameras, specialized behavioral assessments, and biological assessment tools was indicated by the participants as an important component to the rescheduling of cannabis:

> *"…one thing I've been intrigued by is the idea of some kind of video-like way of determining if people are impaired. So, I know NORML helped to work on DRUID [app] which tests your own baseline. Then after you use cannabis, you know you would fail all of these tests. And I heard from a legislator that maybe Carnegie Mellon, there's some university that's working on something like that and I would love to see something like that because then you don't need every officer trained, necessarily. You could potentially just have the results of these tests and your observations don't matter as much because it could all be recorded. So, if something like that could be developed, that would be reliable and could be different for different substances, I think it would be really helpful."*
>
> *"…I also think that we need better tools and some of these new apps may be very helpful, especially if people got used to testing themselves and they made the decision like having the baseline and then making the decision that you know 'I'm impaired. I shouldn't go out and drive now.'"*
>
> *"I think that would be fantastic to do, but I also think they would help the officer at the roadside because no matter what, Speaker 3, no matter what we do to make a standardized DRE [Drug Recognition Expert protocol] and done the same way and even now bodycam and all those things you know the officer's in a position of power. And so the dynamics of that to have an another objective tool available to provide evidence I think would be very help helpful to the officer and to the adjudication."*
>
> *"I'm on a lot of commissions trying to get oral fluid changed in the law. It will help you a lot because it'll reduce the time the officer has to go to the hospital and get blood drawn and meanwhile the THC is not detectable cause it's dropping so quickly and you know it'll mean you're on the road doing your job rather than sitting in a hospital two to three hours trying to get blood samples et cetera. But it's a long process and we're so, so slow."*
>
> *"We need more officers. We need more training. All of that. I am still very strong on toxicology is a necessary confirmation… So, there are tools that go hand in hand. There's no one answer and we need to come up with the combination of testing that*

ensures that we're able to detect impaired driving, but that we don't falsely accused people of impaired driving."

"We absolutely need the documentation of impairment, and the toxicology suggests what drugs may be contributing to that impairment. OK, I'm a huge, huge believer in oral fluid because oral fluid can be taken right at the roadside, non-invasively by the officer and can indicate potentially what drug may be available. And it was interesting, most people think of oral fluid as a providing the probable cause. MMM… I kind of think that officer has a lot of other clues that also provide that, but I think oral fluid gives you a great answer and great support to the officer."

"I think any tool that an officer can have, whether it be an oral fluid tester or a PBT [preliminary breath test] for alcohol is great. But the real-world observations, what their eyes look like speech, odor, admission, all those things, that's the true capture of any kind of impairment. So I don't know if that answered your question. I think we need necessary tools. Training is probably gonna be the biggest thing."

Core Category: Perception and Understanding

As evident from the themes and comments above, perception and understanding is a core concept, encompassing various misunderstandings and confusions related to cannabis use, particularly in the context of its rescheduling (and illustrated in Figure 2). Perception and understanding are driven by, as well as have an impact on:

(a) communication and messaging—lack of consistent messaging generates confusion and distorts perception;

"I think a lot of people don't really understand what rescheduling means, and I think that can also play a huge role in perceptions and later behaviors."
–Focus Group Participant

(b) existing valid research and what resources (funds) are being sourced to understand cannabis use as it relates to public health and traffic safety; and

(c) effective assessment, as the methods and tools used to evaluate impairment directly influence public attitudes and beliefs about cannabis safety and risks.

According to participants, differences in perception and misunderstanding of what the rescheduling of cannabis would mean to the public will be a core issue. Panelists were concerned the public would perceive the rescheduling as an indication that "[cannabis] is safe," increasing the likelihood that cannabis-related negative health and safety consequences would increase. A strong campaign to clarify the meaning of moving cannabis to a lower schedule level in the Controlled Substances Act will be needed to correct any misconceptions about the policy change.

Synthesis

In this section, a structured interpretation of the themes and core findings obtained from participants' opinions is offered, organized under several key questions.

What did the focus group participants say about cannabis rescheduling in terms of impact on public health?

Participants felt that public health impacts would be minimal or lacked certainty around the rescheduling of cannabis. They did speak to a few problems and benefits as a result of this potential federal scheduling change in the Controlled Substances Act.

Most participants agreed that the main concern coming from the rescheduling relates to how the public would perceive the rescheduling. Panelists were concerned the public would perceive the rescheduling as an indication that "*it [cannabis] is safe*," increasing the likelihood that cannabis-related negative health and safety consequences would develop. One participant addressed this well with the following quote: "*That's what my big worry from a public health standpoint…is…Does that message change and cause more people to be willing to experiment, particularly at younger ages, where it may have more impact on the developing brain?"* Participants said that a strong campaign to clarify the meaning of rescheduling cannabis to the public would be necessary to correct any misconception about the policy and the effects of cannabis on the body.

On the other hand, participants agreed that the rescheduling would allow researchers to fully study the public-health consequences of cannabis. This is because federal restrictions on the type and strength of cannabis allowed to be used in federally funded research has limited the types of research that can be conducted. Some participants believe that the beneficial impact on cannabis research would be negligible, arguing that the key research on cannabis has already been conducted.

What did the focus group participants say about cannabis rescheduling in terms of impact on traffic safety?

Experts suggested that cannabis rescheduling would have an impact on traffic safety, largely because by perceiving that "[cannabis] is safe" the rescheduling would translate into an increase in the unsafe use of cannabis among drivers. Participants were concerned that such an increase in cannabis use would occur during a time when methods to establish and detect cannabis impairment still need improvement. As such, the majority of experts spoke to their concern for assessing cannabis impairment, particularly during roadside evaluation. Experts spoke to the tools, such as oral fluid testing and police trained in drug detection assessments, that are currently being utilized, the misunderstandings around toxicology, and the need for continued training for officers who are evaluating cannabis impairment.

The experts agreed that a major concern is polydrug use. They indicated that cannabis is seldom the sole drug being assessed in a traffic safety stop. There is currently a lack of understanding in the research community around polydrug use that includes cannabis and how it impacts traffic safety.

The experts overwhelmingly supported continued research to understand both cannabis-only use and its cognitive impact and impairment associated with driving. Participants also supported research to develop more tools to assess impairment and continued training efforts for law enforcement officers who are evaluating impairment during a roadside stop.

Who is most at risk as cannabis rescheduling is considered?

Focus group participants discussed a lifespan perspective when considering who might be at greatest risk from a rescheduling of cannabis. Consideration was given to the impact on a fetus, young children, adolescents, young adults, and aging adults. A consensus formed that aging adults were at lower risk. These were individuals who were described as 60 years or older. Participants indicated an increase of cannabis use among this group as states legalized the substance and also noted the possible implications of contraindications with other medicine that individuals are prescribed. The experts were nearly unanimous in agreement that the most vulnerable group with regard to the rescheduling of cannabis at a federal level would be young adults, children, and adolescents.

Considering the prevalence of use for youth and adolescents, experts spoke to the impact cannabis use may have on the developing brain and the public health impact of cannabis on children and young adults. The experts noted their concern for youth and adolescent cannabis use perpetuating negative impacts throughout the life of someone who engages in cannabis use at an early age. For example, participants addressed the research that indicates that cannabis use early in life is associated with adult diagnosis of cannabis use disorder. In addition, the groups discussed research related to cannabis use among young individuals that are genetically predisposed to psychiatric disorders. The concern around the developing brain is that the early onset of cannabis exposure would increase the likelihood of a psychotic break, leading to a host of public health impacts.

They also spoke to the limited experience that adolescents and young adults have as drivers and how that could impact traffic safety as a result of the expected increase in cannabis use after the rescheduling of cannabis.

What do the experts say we need to do?

- We need federal-level vision and mission clarification on cannabis rescheduling and/or legalization that is not aligned to political efforts, big pharma, or the cannabis industry. Rather, these efforts need to align to research so that we are promoting a unification of our efforts at the local, state, and federal levels. This unification will allow for uniform messaging that is multiplied by existing written law/policy, law enforcement, educators, researchers, scholars, and medical professionals, among others.
- We need to be transparent, clear, and effective in our communication and messaging rollout. These things need to be linked to data-driven, empirical findings based on both past and current research.
- We need to hyper-focus our messaging around the impact of cannabis on the developing brain.
- We need to continually invest and fund research on the various types of cannabis use and policy impacts.
- We need to consider medical training and how that aligns to current research and messaging.
- Regarding traffic safety, research is needed to continue to explore tools and trainings to assess cannabis impairment.
- We need training for Drug Recognition Experts (DREs) and law enforcement officers to properly assess cannabis impairment, utilizing data-driven and research-based tools and best practices.

- We also need to strengthen the adjudication process for the prosecution of cannabis and other drug-impaired drivers.

Discussion and Conclusion

As described, two focus group sessions were conducted to gather expert opinion on the impact that the rescheduling of cannabis could have on public health in general, and traffic safety in particular. An important feature of this qualitative study was the eliciting of opinions from experts with opposing points of views regarding both the benefits and problems associated with cannabis use. Such a composition of experts allowed a thorough and candid, as well as respectful, treatment of potential challenging issues.

To facilitate the interpretation of the discussion, as noted previously, panelists were instructed to (a) discuss the impact that rescheduling cannabis would have on public health in general, separate from what the impact rescheduling would have specifically on traffic safety; and (b) focus on the impact of rescheduling, not on legalization.

While panelists tended to follow these suggestions, the analyses show that they did not always keep the suggested separations. For instance, when referring to the impact of cannabis on public health, they sometimes had traffic safety in mind. Four categories emerged from the grounded theory analysis of qualitative data:

1. Lack of Prosecution Follow Through
2. State Testing and Regulation
3. Strengthening Adjudication System
4. Distinction from Alcohol Impairment

These were central to the experts' views about the impact of rescheduling cannabis on traffic safety, but these codes fit into a category of Misalignment in Communication & Implementation, which subsumed both traffic safety and public health concerns. The need for an accurate detection method of cannabis impairment at roadside and the need for proper prosecution and adjudication of cannabis offenses have already been abundantly identified as key challenges to the traffic safety community (Smith et al., 2019, Banta-Green & Williams, 2016). Thus, although they were discussed as categories relevant to the general discussion of the effects on cannabis rescheduling, this research team notes that when discussing these specific issues, the panelists were referring to traffic safety outcomes. For consistency and analytical rigor, four categories are presented that pertain to both traffic safety and public health in general, because that is how they were revealed by grounded theory analyses. When interpreting these results, the reader should consider the possibility that participants were referring specifically to traffic safety outcomes.

Although interesting from an academic perspective, the issue of whether these four categories should be considered as characteristics pertaining to public health in general or traffic safety in particular is of negligible practical importance, for it does not affect the focus groups' main result.

Prior to conducting the focus group sessions, it was expected that some of the participants would hold divergent positions and arguments regarding the rescheduling of cannabis. Indeed, recruited experts represented a wide spectrum of opinions about the role of cannabis on our society. Such a strategy was believed to result in a rich and fresh exchange of ideas and opinions; however, despite experts differing on some issues, the study revealed an unexpected homogeneity

regarding experts' opinions. The experts universally agreed that the main challenge to public health and traffic safety from the potential rescheduling of cannabis lies not in the actual rescheduling per se, but in how the public perceives the policy. As revealed by our analysis, misperception and misunderstanding of cannabis rescheduling lie at the core of the issue. The experts agreed that the public seems to misunderstand what a rescheduling of cannabis means. Panelists were concerned the public would perceive the reduction in the Controlled Substances Act schedule level as an indication that "cannabis is safe;" a misconception that would induce an increase in cannabis use, potentially leading to related negative health consequences. For instance, all panelists, regardless of their views about the number of benefits associated with cannabis use, agreed that an increase in the prevalence of driving while impaired by cannabis would be an undesirable consequence of the public's misperception about the safety of cannabis. In other words, the experts were not concerned as much about the rescheduling of cannabis per se as they were about the public misperception about the change in policy that could induce many to misuse cannabis.

As a result, the experts uniformly expressed the need to fight such a misconception. The experts agreed on the core finding of this qualitative study and, accordingly, recommend that compelling, consistent campaigns to clarify the meaning of rescheduling cannabis at the federal level would be necessary to correct any misconception about the policy.

The existence of disparities in public health and traffic safety has been well-documented. These disparities have been associated with a disproportionate risk for marginalized communities, particularly those of color (Cornado, et. al., 2020, Retting, 2021). Despite our efforts to recruit experts with backgrounds as diverse as possible, minorities were minimally represented among study participants. Subsequently, although the depth of expertise and knowledge of those who participated in the focus group sessions is a strength of this study, the limited discussion on the impact a rescheduling of cannabis may have on minorities is a study limitation.

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Appendix A: Focus Group Guide

Rescheduling of Cannabis Focus Group Protocol

Opening

Good afternoon/morning and thank you for being here. As you read in our invitation, this focus group is a research study conducted by the Pacific Institute for Research and Evaluation on behalf of the AAA foundation. Our goal is to elicit expert opinions on the possible outcomes (both favorable and unfavorable) of rescheduling cannabis. We are interested in understanding what impacts the rescheduling of cannabis would have on a variety of public health outcomes (mental health, physical health, and injuries) with special interest on traffic safety.

To achieve this goal, we will ask the group their opinion on public health outcomes not related to traffic safety as well as outcomes that are related to traffic safety.

This session is anonymous. Your individual insights are utilized to generate thematic analysis and no individuals will be identified as we report our findings.

To stay present in the dialog while also securing an accurate transcription of our conversation, this meeting will be recorded. The recording is for transcription purposes and all identifiable information will be removed from the transcription. Once the transcription is completed and de-identification has occurred, the original recording will be destroyed.

Do I have everyone's permission to continue with the transcription recorder on?

Community engagement – while we are together, we may disagree with one another. We encourage everyone to share and ask that we give grace to each participant while honoring these fundamental community rules:

- Safe space, no judgements and confidentiality honored
- Strong opinions, loosely held
- Disagree without being disagreeable
- Seek to understand, as well as to be understood
- Tackle the issue, not the person
- Everyone participates, no one dominates
- ELMO (enough, let's move on)

Anything we missed or that you would like to add

Brief Introductions? Tell us a little about yourself.

Let's start with public health outcomes that are not related to traffic safety. This may include physical health, mental, health and injury related outcomes.

Walk me through a rescheduling of cannabis. What impacts does this have on public health? Please be specific on which areas of public health. Please mention the population groups you expect to hurt and those you expect to benefit the most

Probes:

- How does the rescheduling align to public health evidence (what we currently know about cannabis)?
- What demographic considerations should we consider (age, location, race/ethnicity, gender, etc.)?
- Differences by states?
- Is there a temporal component to rescheduling? For example, how might this evolve over time?
- Staying with public health outcomes that were discussed, talk to the likelihood of these outcomes. Please discuss prevalence.
- Considering some of the negative outcomes discussed, what policies or mitigation measures do you propose to consider?

Thank you for the robust discourse on public health outcomes. I would like to move us into a discussion on traffic safety as it relates to a rescheduling of cannabis. Similar to the previous discussion, we would like to learn about possible scenarios, their likelihood, and differences among groups for a rescheduling on cannabis as it specifically pertains to traffic safety.

What would this look like?

Probes:

- How does rescheduling impact law enforcement? Are there detection considerations for law enforcement?
- What demographic considerations should we consider (age, location, race/ethnicity, gender, etc.)?
- Differences by states?
- Is there a temporal component to rescheduling's impact? For example, how might this evolve over time?
- Exclusively considering traffic safety outcomes that were discussed, talk to the likelihood of these outcomes. What is the prevalence of these outcomes?
- Considering some of the negative outcomes discussed, what policies or mitigation measures do you propose to consider?

Closing Remarks

Again, I want to thank you for your time and shared understanding of the rescheduling of cannabis. These data will be analyzed, and an unidentified report of the findings will be generated. We will be sure to follow up with each of you once that process is complete. In order to validate the work we did today, would you agree to allow me to send you a copy of the de-identified transcript and ask you to briefly review it for accuracy?

Appendix B: Participant Invitation

I am writing to invite you to participate in virtual discussion group on the topic of cannabis use. We need your expertise!

In 2017, a committee of experts gathered by the National Academies of Sciences, Engineering, and Medicine (NASEM) was tasked with conducting a comprehensive review of the evidence regarding the health effects of using cannabis and cannabis-derived products. The NASEM study reported that the scientific information on the health implications of cannabis use was uneven, with areas of varying gaps in knowledge.

Using the 2017 NASEM report as a starting point, the Pacific Institute for Research Evaluation (PIRE), on behalf of the AAA Foundation for Traffic Safety (AAAFTS), conducted a review of the literature aimed to summarize the current state of scientific knowledge on cannabis use as it is associated with the factors established by the Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act, or CSA for short) for drug scheduling. Broadly speaking, the review concluded that despite some scientific progress, conclusive information on certain public health implications associated with cannabis use is still lacking.

As a result, AAAFTS and PIRE would like to elicit the opinion of well-known experts on the public health implications relevant to the scheduling of cannabis that remain inconclusive. We would also like to explore the effects a potential rescheduling of cannabis in the U.S. to a lower level might have on a variety of clinical and public health fields, including but not limited to traffic safety.

Your contribution will be confidential when the data are analyzed and reported thematically. Quotes may be referenced; however, no individual names will be associated with data collected. During the focus group discussion, the researcher will record for transcription purposes only. PIRE staff, Dr. Ann Romosz, will be leading the discussion. Other PIRE staff in attendance include me and Dr. Eduardo Romano.

As a token of appreciation for your time and input, we are offering a $100 amazon gift card for all who attend a focus group session. If you are available to participate, please let us know which of the following times would be best for you to have a virtual approximal 90-minute discussion?

Monday, May 20th 3 pm – 5 pm EST OR Friday May 24th 10 am – 12 pm EST

Once we have your preferred time, we will send you a Microsoft Teams link for joining this important, scientific discourse.

Thank You.

Appendix C: Codebook (Description of Codes)

Code Name	Totals	Description
Benefits of Cannabis Rescheduling for Health Issues or Other Reasons	13	Participant discusses potential benefits to cannabis use for medicinal purposes. Participant may also discuss benefit of cannabis for financial (tax) purposes or education.
Cannabis Dosing	10	Knowing how much you have had. This could also include increasing amount ingested (dosing over days, weeks, months, etc.).
Cannabis Marketing	6	Participant speaks to how cannabis is marketed and sold.
Cannabis Rescheduling is a Process	3	Cannabis rescheduling will happen but a process exists.
Cannabis Rescheduling Proactivity	3	Being ahead of the process; proactive; not reactive.
Define Cannabis Rescheduling Process	7	Steps to occur.
Cannabis Types	14	There are varies types of cannabis flowers and ways of ingesting. What is being considered in the rescheduling is questioned.
Cannabis Use Linked to Mental Health or Other Medical Disorders	6	Participant speaks of cannabis use in conjunction with mental health disorder.
Cannabis User Care of Rescheduling	3	What will the average user think of rescheduling.
DRE	8	Participant speaks of DREs when discussing traffic safety and cannabis use.
Doctor Comfort w/ Cannabis Conversations	3	Participant discusses primary care providers comfort level with discussing or prescribing cannabis.
Drug Dependency	1	Dependence on drug.
Drug Potency	12	Participant references the potency of cannabis.
Funding/Resourcing	3	Participant speaks to funding or resources toward cannabis research.
Lack of consensus	1	Non-agreement.
Links to Reporting Data	3	Participant speaks about how rescheduling, or legalization relates to reporting use.

Code Name	Totals	Description
Localized Public Health Tactic	2	A tactic that is being implemented at a local level, not state or federal.
Marginalized Communities Distinctions	4	This could include a reference to race, ethnicity, sexual orientation, gender, etc.
Meaningful Reclassification Suggestion	1	We should be doing more '-' (Fentanyl provided as one example).
Messaging	4	How the change is messaged is addressed.
Coordination of messaging/roll out	19	How messaging should be handled around cannabis rescheduling.
Negative perception of messaging	9	Past errors in messaging.
Misaligned Thinking	2	"Out of step" not common thinking or against the norm in some way.
Normalization of Cannabis Use	2	Process by which the drug becomes less stigmatized and more accepted.
Polydrug use	13	implications around using more than one substance simultaneously.
Prevalence and Availability of Cannabis	11	Participant discusses rescheduling impact on prevalence and availability of cannabis.
Problem: Contraindications	3	Cannabis use with other medicine. How might the drugs interact?
Problem: Crime Outcomes Associated with Cannabis Rescheduling	2	Any criminal offense associated with cannabis rescheduling.
Problem: Misunderstanding of Rescheduling	12	Public does not understand rescheduling; sometimes spoken in reference to legalization.
Problem: Perception of Harm Decline	10	With rescheduling and legalization, the perception of harm for cannabis use is declining.
Problem: Rescheduling Cannabis Misalignment	11	Laws are not aligned at federal and state level.
Problem: Rescheduling Cannabis on Developing Brain	12	How does cannabis use impact the brain in development.
Public Health Change	0	Assessing change to public health.
PH Change - No	12	No belief in change; minimal impact of cannabis rescheduling to public health.

Code Name	Totals	Description
PH Change - Yes	7	Identifies that change will result from cannabis rescheduling '-' child codes to determine type of change.
PH Change - Uncertain	4	Not convinced, unsure, could argue both sides.
Questioning Possibility of Rescheduling of Cannabis	1	Does not believe that the rescheduling will be implemented; doubts execution.
Research Reference	22	Research opportunity as an outcome of rescheduling considered. Research might be challenged. Research used to support point.
Responsibility of Choice	3	People make choices with regard to cannabis use.
Misunderstanding of Cannabis	10	Refers to public perception that might be incorrect or limited in some way.
Role of Federal Gov't	1	Participant speaks to the part the federal government plays in rescheduling.
Gov't Institutional Mistrust	11	Role of federal government is questioned due to original scheduling of cannabis as a category 1. The perception of the public's trust of the government is called into question.
State Testing and/or Regulation	7	Participant speaks to specific state tests, laws, regulations and notes distinction between other states or federal govt.
Traffic Safety Implications of Rescheduling	1	Parent code for traffic safety.
Assessment: Cannabis Impairment	22	Participant speaks to roadside assessment (tools, behavior, the ability to assess with confidence around a driver's level of influence). How do we measure impairment?
Accident to Incident	1	Change in language around cannabis use and resulting outcomes.
All impaired Driving is Bad	3	Impaired driving of any kind is thought of as bad, dangerous, etc.

Code Name	Totals	Description
Concern for Cannabis Impaired Driving to Deplete Resources	1	Will cannabis impair driving take resources away from alcohol impaired driving mitigation efforts?
Distinction from Alcohol Impairment	10	Participant compares and makes distinction from cannabis to alcohol.
Employment and Cannabis Use	2	How might this impact work functioning as cannabis is rescheduled and people may consume it for medicinal purposes?
Increase in DUI	2	Participants suggest increase in DUI as a result of rescheduling.
Lack of Prosecution Follow Through	3	Participant speaks to lack of (decline in or otherwise) of prosecution of cannabis cases.
Per Se	2	Latin for "by itself" and references the law that a BAC over the legal limit is enough to pursue conviction.
Rescheduling no impact on traffic safety	1	Lack of impact on traffic safety specifically due to rescheduling.
Suggestion: Strengthen Adjudication System	7	Participant either speaks of ideas to strengthen the adjudication system or addresses what is lacking or problematic about it now.
Traffic Safety Data on Impairment	5	Current information and data on driving under the influence of cannabis is discussed.
Younger Drivers and Cannabis Use	2	Participants discuss young drivers, lack of experience, etc.
Value Assessment on Cannabis Use	5	Participant speaks of their belief system related to cannabis use. This is not a reflection of science or public health but rather a value/belief comment.