[Insert Pun Here]: What the DOJ's Efforts to Reschedule Medical Marijuana Means for Alabama and Multistate Employers

Presented by:

Tae Phillips

Ogletree, Deakins, Nash,

Smoak & Stewart, P.C.

tae.phillips@ogletree.com

205-714-4409 (Direct Dial-Office)

Best Lawyers LAW FIRM OF THE YEAR U.S.News & WORLD REPORT LITIGATION – LABOR & EMPLOYMENT 2021

Atlanta
Austin
Berlin
Birmingham
Boston
Charleston
Charlotte
Chicago
Cleveland
Columbia
Dallas
Denver
Detroit (Metro)
Greenville
Houston
Indianapolis
Kansas City
Las Vegas
London
Los Angeles
Memphis
Mexico City
Miami
Milwaukee
Minneapolis
Montréal
Morristown
Nashville
New Orleans
New York City
Oklahoma City
Orange County
Paris
Philadelphia
Phoenix
Pittsburgh
Portland (ME)
Portland (OR)
Raleigh
Richmond
Sacramento
San Antonio
San Diego
San Francisco
Seattle
St. Louis
St. Thomas
Stamford
Tampa
Toronto
Torrance
Tucson
Washington D.C.

Ogletree Deakins

What Should Employers be Worried About?

- The One Where Everyone (In Our Company) Has an Opinion
  - (a/k/a What Should We Do?)
- The One with Testing Challenges (Who, When, What, How?)
- The One Where We Are Concerned About Safety (Drugs, Alcohol and Marijuana are Impairing, Right?)
- The One with the Marijuana Laws (The Legalization Laws Themselves)
- The One with the Drug/Alcohol Testing Laws
- The One that Brought Up Off Duty Conduct (i.e., Smoking Marijuana Outside of Work)
- The One Where We Get Sued for Disability Discrimination

Ogletree Deakins

Inevitable Concerns and Questions

- Navigating Stakeholder Opinions and Servicing Internal Clients (EHS, Operations, HR, Etc.)
- Testing Program
- How Do We Keep the Workplace Safe
- There are Laws. So We Need to Comply with the Law, Right?
- Do We Want to Regulate What People Do Outside of Work?
- How Do We Avoid Being Sued?
- How Do We Protect the Company's Interests With Regards to Unemployment, Workers' Comp, OSHA, etc.
- How Can We Recruit and Retain?
- Wait . . . Isn't Marijuana Illegal Under Federal Law? That Matters Right?

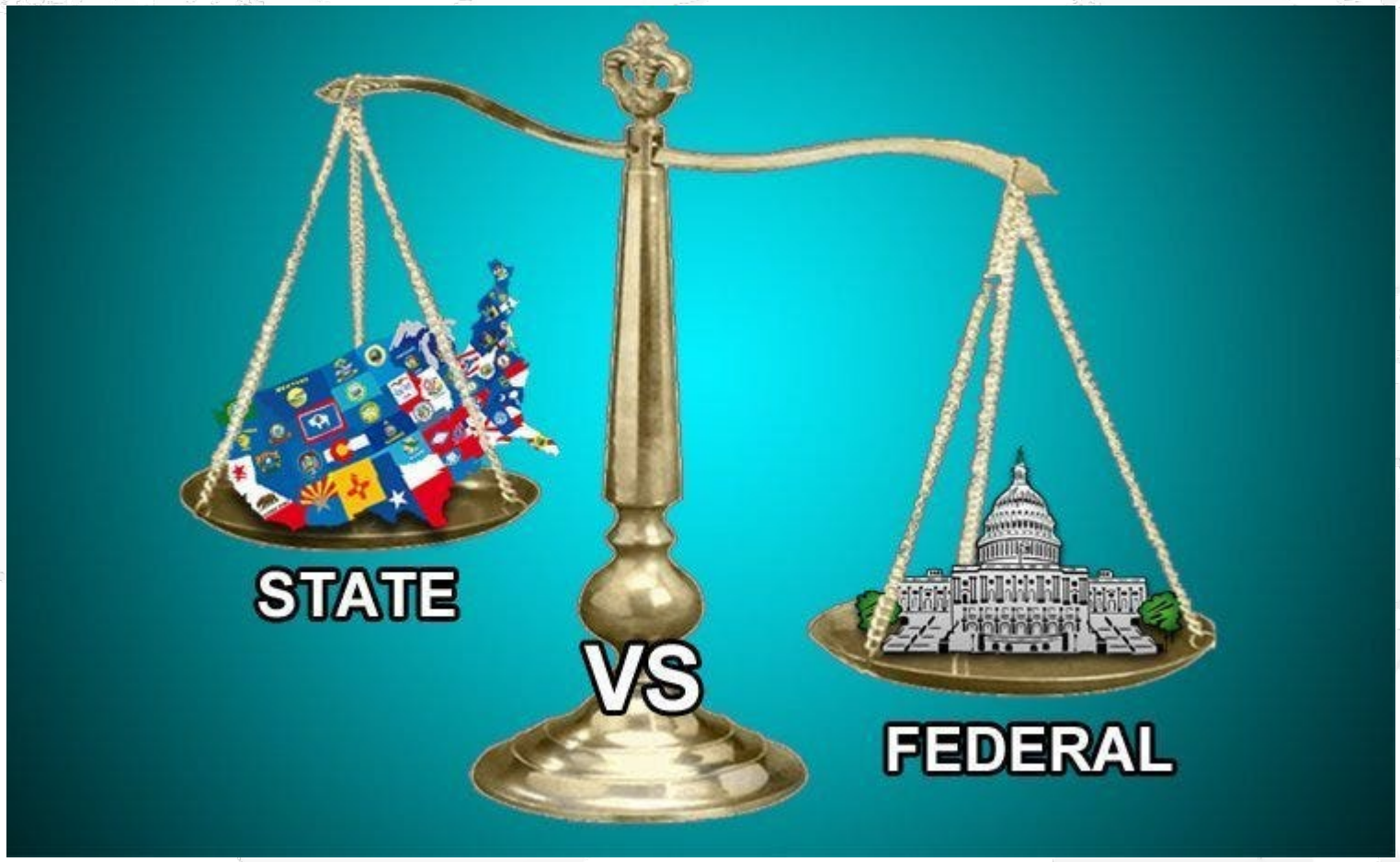
Ogletree Deakins

Introduction and Agenda

- The Controlled Substances Act
  - Rescheduling Efforts – 2024 Edition
  - Rescheduling Efforts – 2025 Edition
  - Rescheduling Efforts – 2026 Edition
- Marijuana in the Workplace 101
- Alabama Medical Marijuana Act
- The Primary Risk: Disability Claims

Ogletree Deakins

Federal Versus State Laws – Always Important!



Ogletree Deakins

The Controlled Substances Act

- Under the Controlled Substances Act, the U.S. Drug Enforcement Administration (DEA) and U.S. Food and Drug Administration jointly classify drugs on a I through V schedule.
- Schedules based on:
  - Potential for abuse
  - Accepted medical uses
  - Potential for addiction

Ogletree Deakins

The Controlled Substances Act (cont.)

- **Schedule I** – No accepted medical use and a high potential for abuse.
- **Schedule II** – Accepted medical use with high potential for abuse and dependence.
- **Schedule III** – Accepted medical use and a moderate to low potential for psychological dependence and a lower potential for abuse than Schedule I.
- **Schedule IV** – Accepted medical use with a low potential for abuse and low risk of dependence.
- **Schedule V** – Accepted medical use with the lowest potential for abuse with limited quantities of narcotics.

Translation: Schedule III is somewhere in the middle.

Ogletree Deakins

Marijuana at the Federal Level – 2024 Edition

- On April 30, 2024 the U.S. Department of Justice circulated a proposal to reclassify marijuana from a Schedule I to a Schedule III controlled substance.

Ogletree Deakins

Marijuana at the Federal Level – 2025 Edition

- On December 18, 2025, President Trump signed an Executive Order directing the Attorney General to reclassify marijuana from a Schedule I to a Schedule III controlled substance.
  - "…to take all necessary steps to complete the rulemaking process related to rescheduling marijuana to Schedule III"

Ogletree Deakins

Marijuana at the Federal Level – 2026 Edition

- On April 22, 2026, Attorney General Todd Blanche signed an Order directing that "drug products containing marijuana that have been approved by the FDA" and "marijuana subject to a state medical marijuana license" be immediately placed on Schedule III of the Controlled Substances Act

- Scheduled a hearing "with respect to the proposed rescheduling of marijuana into Schedule III of the CSA beginning June 29, 2026" in order to "provide a timely and legally compliant pathway to evaluate broader changes to marijuana's status under federal law."

Ogletree Deakins

Marijuana in the Workplace 101

- Four Things to Remember:
  - 1. Marijuana Laws are Very State Specific
  - 2. Marijuana Laws Change Often
  - 3. Marijuana in the Workplace: Broader and More Complicated Than You Think
  - 4. Marijuana in the Workplace: Sometimes it is Misleading

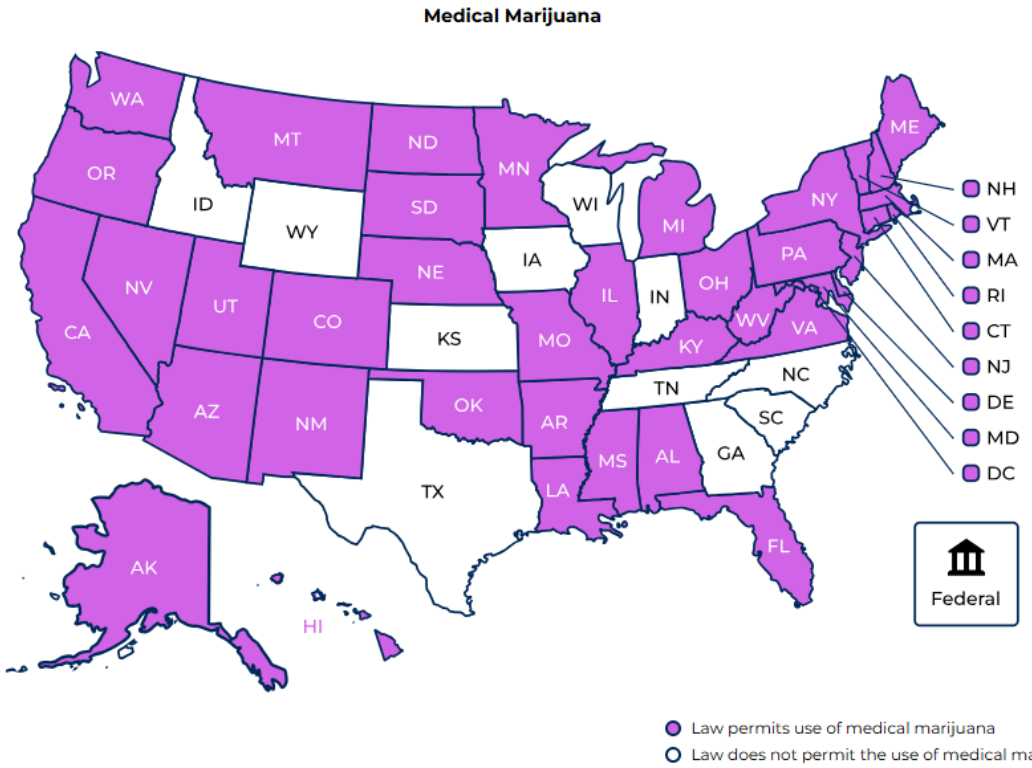
Ogletree Deakins

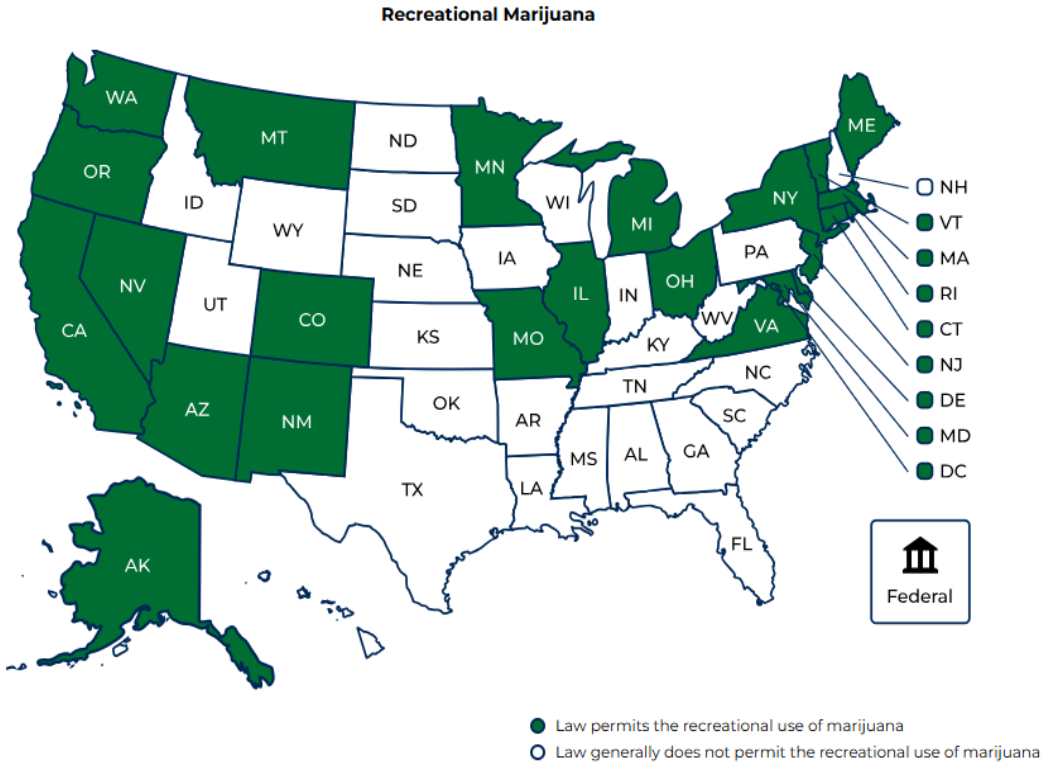
Marijuana in the Workplace 101

- BUT….
  - 5. You Have More Control And Flexibility Than You May Think

Ogletree Deakins

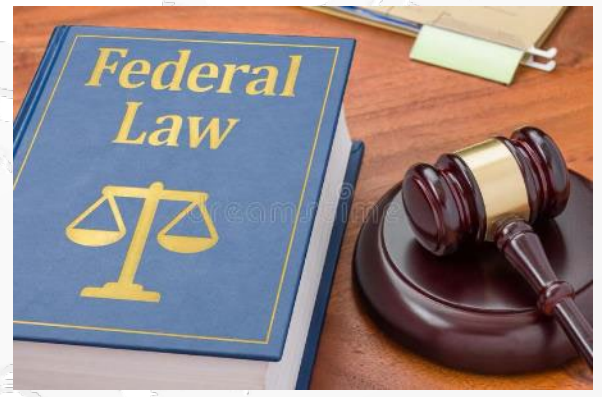
Marijuana in the Workplace 101: The Laws are State Specific…and Change Often





Ogletree Deakins

Marijuana 101 - So Complicated (it will make you want to Burn One Down)



Ogletree Deakins

Marijuana 101: Sometimes Misleading

- Marijuana = Impairing
- Drug Tests Cannot Measure or Establish Impairment
- Marijuana is Not Prescribed
- Government Contractor Status: Irrelevant
- OSHA Obligations: Sort of Irrelevant
- DOT-Regulated Positions (and other federally-regulated positions) are Under a Different Framework
- Marijuana Laws . . . Not the Same as Drug Test Laws

Ogletree Deakins

Marijuana 101 - Types of Legal Claims

- (1) – Violation of a State Marijuana Legalization Law
  - "Did the employer violate the marijuana law itself?"
- (2) – Disability Discrimination
  - "Did the employer discriminate against a medical marijuana cardholder because of an underlying disability?"
  - Did the employer fail to accommodate a medical marijuana cardholder?
- (3) – Lawful Off-Duty Conduct Laws
  - "Did the employer take adverse action against an individual based on otherwise lawful activity outside of work?"

Ogletree Deakins

Marijuana at the Federal Level – 2026 Edition

- On April 22, 2026, Attorney General Todd Blanche signed an Order directing that "drug products containing marijuana that have been approved by the FDA" and "marijuana subject to a state medical marijuana license" be immediately placed on Schedule III of the Controlled Substances Act

- Scheduled a hearing "with respect to the proposed rescheduling of marijuana into Schedule III of the CSA beginning June 29, 2026" in order to "provide a timely and legally compliant pathway to evaluate broader changes to marijuana's status under federal law."

Ogletree Deakins

Non-Employment Consequences of Rescheduling

- Research
- Banking
- Taxation
- Criminal Issues
- Potential FDA Oversight?
- Prescribe-ability?

Ogletree Deakins

Employment Consequences of Rescheduling

- State Laws --- Still Apply
- Marijuana --- Still Not "Legal"
- Employers --- Still Can Prohibit Use, Possession, or Impairment at Work
- Employers --- Still Can Take Adverse Action in Many Circumstances

- Biggest Impacts:
  - 1. Potential Rise of ADA Claims
  - 2. If Marijuana Can Be Prescribed…
  - 3. DOT-Regulated Employees

Ogletree Deakins

Alabama's Medical Marijuana Law --- What a Long Strange Trip It's Been

Ogletree Deakins

What Does the AL Medical Marijuana Law Say?

- Qualifying Medical Conditions:
  - Autism Spectrum Disorder
  - Crohn's Disease
  - Depression
  - Epilepsy
  - HIV/AIDS-related Nausea or Weight Loss
  - Panic Disorder
  - Parkinson's Disease
  - PTSD
  - Sickle Cell Anemia
  - Spasticity
  - Tourette's Syndrome
  - "Condition Causing Chronic Pain"
  - "Terminal Illness"
  - "Persistent Nausea"
  - "Cancer-Related Nausea, Weight Loss, Chronic Pain"

Ogletree Deakins

What Does the AL Medical Marijuana Law Say?

- No Employment Protections for Medical Marijuana Cardholders (within the Medical Marijuana Law Itself)

- Possible Disability Discrimination or Disability Accommodation Issues?
  - Medical Marijuana Cardholder Status = Qualifying Medical Condition = Disability
    - AL does not have a state disability discrimination law and, instead, would be governed solely by the Americans with Disabilities Act of 1990

- Does Not Allow for Smoke-able Forms of Marijuana or Marijuana-Infused Food Products
  - Only oils, creams, patches, pills, lozenges, etc.

Ogletree Deakins

What Does the AL Medical Marijuana Law Say?

- Employer-Friendly Language – The Medical Marijuana Law Does Not:
  - Require employers to permit, accommodate, or allow the use of medical marijuana
  - Require an employer to modify job or work conditions for applicants or employees who use medical marijuana
  - Prohibit employers from establishing and enforcing drug testing, drug-free workplace, etc. policies
  - Prohibit employers from requiring medical marijuana cardholders to notify employers of medical marijuana cardholder status
  - Interfere with federal regulations or restrictions, such as DOT regulations
  - Provide for an express, legal cause of action for an individual to file a claim against an employer for taking adverse employment action due to medical marijuana use

Ogletree Deakins

How Will Courts Interpret the AL Medical Marijuana Law? What Should Employers Be Worried About?

Ogletree Deakins

Medical Marijuana and Disability Issues?

- "Disability" (ADA definition)
  - A physical or mental impairment that substantially limits one or more major life activities
  - A person who has a history of a physical or mental impairment that substantially limits one or more major life activities
  - A person who is perceived by others as having a physical or mental impairment that substantially limits one or more major life activities

Ogletree Deakins

(Real Life) Case Study

Ogletree Deakins

(Real Life) Case Study

Ogletree Deakins

(Real Life) Case Study

Ogletree Deakins

(Real Life) Case Study

Woman fights medical marijuana | Mass. Woman Fired For Using M

cbsnews.com/boston/news/mass-woman-fired-for-using-medical-marijuana/

LOCAL NEWS ›

Mass. Woman Fired For Using Medical Marijuana

CBS NEWS BOSTON

SEPTEMBER 17, 2015 / 10:20 PM / CBS BOSTON

BOSTON (CBS) - Cristina Barbuto started a great new job last year.

It lasted one day.

Woman fights medical marijuana | Mass. Woman Fired For Using M

bostonglobe.com/metro/2015/05/22/medical-marijuana-patient-files-discrimination-complaint-over-firing/iptEJe2A0TITWuoJggQgZL/story.html

Woman fights medical marijuana firing

Case exposes paucity of guidelines for workers and bosses, lawyers say

By Kay Lazar Globe Staff, May 22, 2015, 10:32 p.m.

100

(Real Life) Case Study

Ogletree Deakins

How Are Companies Handling These Issues?

- Drug/Alcohol Testing
- Marijuana Testing

Ogletree Deakins

All Right, All Right, All Right -- Best Practices

- Figure Out What You "Want" To Do
  - *Who, What, When, Where, How?*
- Good Documentation and Infrastructure
  - *Policies*
  - *Checklists*
  - *SOPs*
- Training
  - *HR*
  - *Manager/Supervisor*
  - *EHS*

Ogletree Deakins

Ogletree Resources

- FREE blogs, webinars, and podcasts
- Training for Managers, Supervisors, HR, and Health/Safety
- Flat-Rate Drug/Alcohol Testing Template Policy
- Flat-Rate Workplace Marijuana Guide
- Client Portal – Ogletree

Ogletree Deakins

Questions

Ogletree Deakins

Thank you!

Tae Phillips

Ogletree, Deakins, Nash, Smoak & Stewart, P.C.

420 20th Street North, Suite 1900 | Birmingham, Alabama 35203

tae.phillips@ogletree.com

Phone: 205.714.4409 (Office) / 205.281.8849 (Cell)

Ogletree Deakins

NATIONAL SAFETY COUNCIL

Position/Policy Statement

Cannabis Impairment in Safety Sensitive Positions

NSC Policy/Position

The National Safety Council (NSC) supports policies to mitigate and eliminate the risks of cannabis (marijuana) and other products containing delta-9-tetrahydrocannabinol (THC), the impairing component in cannabis. Safety concerns are paramount as legalization and decriminalization continues.

NSC believes it is unsafe to be under the influence of cannabis while working in a safety sensitive position[1] due to the increased risk of injury or death to the operator and others. Research is clear that cannabis impacts psychomotor skills and cognitive ability. However, the amount of THC detectable in the body does not directly correlate to a degree of impairment. At this time, NSC believes there is no level of cannabis use that is safe or acceptable for employees who work in safety sensitive positions.

Need for Policy Position

By adopting this position, NSC will be able to increase involvement in the policy discussion about cannabis impairment, and provide guidance for employers as they navigate changing cannabis laws.

Cannabis is the most widely consumed illicit substance worldwide.[2] In 2015, the World Drug Report estimated over 200 million people between the ages of 15-64 have ingested cannabis. According to a study reported by the National Institute on Drug Abuse, employees who tested positive for cannabis had:

- 55% more industrial incidents
- 85% more injuries
- 75% greater absenteeism compared to those who tested negative.[3]

---

[1] "Safety Sensitive" refers to jobs that impact safety of the employee and the safety of others as a result of performing that job. For example, 49 CFR §382.107 defines safety sensitive for commercial motor vehicle operators.
[2] https://www.who.int/substance_abuse/facts/cannabis/en/
[3] NIDA. "Marijuana." *National Institute on Drug Abuse*, 25 Jun. 2018, https://www.drugabuse.gov/publications/research-reports/marijuana. Accessed 30 Apr. 2019.

Cannabis affects the body in a number of ways. Experimental studies of subjects dosed with cannabis found, psychological effects include relaxation, sedation, disorientation, impaired judgment, and lack of concentration. The physiological effects include slowed fine motor skills, reddening of eyes, increased appetite, dry mouth, and increased heart rate. These effects contribute to impaired learning, short-term memory and attention deficits, and delayed decision-making.[4]

As a leader in impairment (opioids, fatigue, etc.) workplace policies and consistent with advocacy in these other areas, NSC supports moving people to non-safety sensitive operational positions when using cannabis for medical purposes.

Federal Law

Despite medical cannabis laws in 46 states, cannabis remains federally illegal. The federal government regulates drugs through the *Controlled Substances Act* (CSA) (21 U.S.C. § 811), which does not recognize the difference between medical and recreational use of cannabis.[5] Under the CSA cannabis is classified as a Schedule 1 drug, meaning that the federal government views cannabis as having no medical value and high abuse potential.

There are no federally approved prescriptions for cannabis use. Doctors may not "prescribe" cannabis for medical use under federal law, however they can "recommend" its use under the First Amendment.

State Laws

Cannabis laws vary from state to state. At the time of writing this document, 3 states, the District of Columbia, Guam, Puerto Rico and US Virgin Islands have approved comprehensive, publicly available medical marijuana/cannabis programs. Twenty-three states and the District of Columbia have decriminalized marijuana, and ten states and the District of Columbia now have legalized small amounts of marijuana for adult recreational use. States that have approved the medical use of cannabis have allowed certain classes of medical professionals to grant a person residing in the state to purchase and use cannabis in certain controlled forms. Those states that have decriminalized or legalized recreational use of cannabis permit a person to purchase and use cannabis if:

- They are in that specific state
- The cannabis is in a legal form with regulated strengths
- It is under the maximum amount allowance, if the law stipulates an amount

Research

More comprehensive data and research is needed to better understand the effects cannabis has on the human mind and body. There are many anecdotal studies on a variety of cannabis-related subjects, including but not limited to assessing and defining the THC relationship to impairment, examining other safety implications, driving, vehicle crash rates, potential medical uses and benefits, impacts on opioid misuse and opioid overdoses, and more. However, there is not enough research to reach consensus on any of these cannabis-related subjects at this time.

[4] NIDA. "Marijuana." *National Institute on Drug Abuse*, 22 Jun. 2018, https://www.drugabuse.gov/publications/drugfacts/marijuana.
[5] https://www.law.cornell.edu/cfr/text/21/1308.11

There is evidence that legalization or decriminalization of cannabis may increase vehicle crash rates, hospitalizations,[6] and other public health indicators. The Rocky Mountain High Intensity Drug Trafficking Area completed a study that found the yearly rate of emergency department visits related to marijuana[7] increased 52 percent after the legalization of recreational marijuana.[8] A study done by the Insurance Institute for Highway Safety (IIHS) examined 2012-2016 police-reported crashes before and after the retail sales of cannabis began in Colorado, Oregon, and Washington. IIHS estimates that these three states combined saw a 5.2% increase in the rate of crashes per million vehicle registrations, compared with neighboring states that did not decriminalize or legalize marijuana sales.[9] In 2017, the NSC Alcohol, Drug and Impairment Division issued "Position on Cannabis (Marijuana) and Driving," which clearly evaluates leading research concluding that cannabis degrades driving performance.[10]

NSC expects support from the American Industrial Hygienists Association, which has a similar position. Companies supporting cannabis decriminalization will oppose the position.

This position statement reflects the opinions of the National Safety Council but not necessarily those of each member organization.

Adopted by the National Safety Council, 2019

[6] https://rmhidta.org/files/D2DF/FINAL-%20Volume%205%20UPDATE%202018.pdf
[7] In this instance, "marijuana" is used as the term for cannabis from the underlying research document.
[8] Ibid.
[9] https://www.iihs.org/iihs/news/desktopnews/crashes-rise-in-first-states-to-begin-legalized-retail-sales-of-recreational-marijuana
[10] https://www.nsc.org/Portals/0/Documents/NSCDocuments_Advocacy/Divisions/ADID/Position-on-Cannabis-and-Driving.pdf

AMERICAN BAR ASSOCIATION
Health Law Section

THE HEALTH LAWYER

IN THIS ISSUE

Volume 29, Number 2,
December 2016

MALPRACTICE LIABILITY AND MEDICAL MARIJUANA

Douglas B. Marlowe, J.D., Ph.D.
National Association of Drug Court Professionals
Chadds Ford, PA

Introduction

As of mid-year 2016, twenty-five states and the District of Columbia authorized the use of raw or botanical marijuana to treat various categories of medical conditions, and an additional fifteen states authorized the use of low-potency delta-9-tetrahydrocannabinol ("THC")[1] marijuana to treat a limited number of medical conditions.[2] These developments reflect a rapidly growing perception on the part of the U.S. public and policy makers that marijuana has proven health benefits.[3] At the same time, however, a large number of national practitioner and scientific organizations have taken official positions against medical marijuana on scientific grounds,[4] a growing number of studies are uncovering serious negative health consequences associated with its use,[5] and evidence supporting its effectiveness is confined to a small cluster of medical conditions.[6]

This apparent disconnect between public policy and scientific knowledge could lead to malpractice exposure or other liability for physicians certifying or recommending marijuana for their patients. Physicians in medical marijuana states do not prescribe marijuana, but rather certify that a patient has a statutorily covered medical condition and meets other criteria to receive a medical marijuana permit or authorization. As will be discussed, this distinction is unlikely to alter the fundamental nature of the doctor/patient relationship or lessen the physician's obligation to render competent professional care.[7]

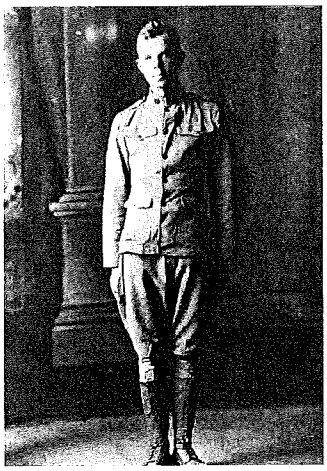
State laws vary considerably in terms of what medical conditions may be treated with marijuana.[8] They also vary in terms of the educational and professional obligations they impose on physicians; however, many states require physicians to receive several hours of continuing education on medical marijuana, personally examine each patient, obtain informed consent from the patient, develop a treatment plan, seek consultation if indicated, review the patient's progress in treatment, and maintain accurate medical records.[9] Failing to abide by the statutory provisions can lead to a loss of medical marijuana certification privileges, professional disciplinary action,[10] and possibly to criminal prosecution.[11] It also provides convincing evidence in a malpractice action that the physician's conduct fell below the requisite standard of care, and may even constitute negligence *per se* (on its face) because the provisions are

continued on page 3

C. Joyce Hall

My Veteran

For a Southern girl, possibly the only relationship to rival the relationship between a girl and her daddy is the bond between a girl and her granddaddy. I introduce you to my grandfather, Allen G. Monroe, pictured here in his WWI uniform. Pawpe, as he was affectionately known to his eight grandchildren, taught us many life lessons that he was quite sure we were not being taught in school—how to ride a horse, milk a cow, plow a mule (well, I walked behind him), pick peas and beans, dig potatoes and shuck corn. But more importantly, my grandfather taught me to fiercely love my family, my friends, my neighbors, and my country. He also taught me to always honor and respect those who fought for the freedom that we enjoy.



Pawpe trained at Camp Beauregard in Louisiana, and he was preparing to be shipped off when Germany signed the Armistice Agreement on November 11, 1918. He never left American soil, but his devotion to our country's military and veterans' affairs never waned. As a recipient of care at the VA medical center, he often visited his friends or family members who were veterans receiving care at the VA. Pawpe watched his son leave for WWII, and he proudly welcomed him home again when the war ended. He listened to his daughter (my mom) deliver her Salutatorian speech at her high school graduation in 1945 entitled "Our Debt to Our Veterans."

How do we measure what we owe to those who have served on our behalf? I submit that their service should be considered and treated as priceless to all of us who bask in the freedom they preserve for us. From a practical standpoint, what can we do as health lawyers to give

continued on page 18

AMERICAN BAR ASSOCIATION Health Law Section

THE HEALTH LAWYER

THE ABA HEALTH LAW SECTION

The Health Lawyer (ISSN: 0736-3443) is published by the American Bar Association Health Law Section, 321 N. Clark Street, Chicago, IL 60654-7598. Address corrections should be sent to the American Bar Association, c/o Member Records.

continued from page 1

intended specifically to protect patients from foreseeable harm.[12]

Physicians may still be sued for malpractice even if they follow the statutory provisions meticulously. Physicians are often sued for malpractice for treatments that are unquestionably lawful and authorized by applicable licensing and regulatory statutes. The dispositive question in malpractice cases is not whether the physician's actions were legally authorized but whether they were performed in accordance with professional standards of care.[13]

No published court opinion has thus far considered the issue of malpractice liability for a physician certifying or recommending the use of medical marijuana. Although there are numerous instances of consumers being injured by other types of botanical products and herbal remedies, most law suits related to those substances have been product liability actions against the distributers or manufacturers of the products.[14] Medical marijuana raises different legal issues from prior cases because patients are usually required by law to receive a physician's approval to use the drug, whereas other herbal products can be obtained readily without physician involvement. In the absence of analogous legal precedent, courts confronting medical marijuana cases will in many respects be writing on a blank slate.

This article provides a review of scientific research on the proven health benefits and health risks of marijuana, and considers how professional malpractice principles might be applied in medical marijuana cases. It is concluded from this review of the medical and legal literatures that malpractice liability will likely depend on several factors, including: (1) what legal test is applied in a given jurisdiction to define the medical standard of care, (2) the extent to which national practice guidelines and scientific studies are admissible as evidence to establish the standard of care, and (3) whether the patient was adequately informed about the potential risks and benefits of marijuana, its relative effectiveness compared to alternative treatments for the patient's condition, and the degree to which scientific evidence and expert consensus support or refute its use. It behooves physicians and health lawyers to familiarize themselves with these principles, consider how they are likely to be applied in their jurisdictions, and take reasonable precautions to avoid or reduce malpractice exposure.

This article does not address the issue of legalization or decriminalization of marijuana for recreational purposes. Every citizen has a right to engage in lawful conduct so long as that conduct does not endanger the welfare and safety of others. Different legal principles apply, however, when learned professionals such as physicians are involved in the decision. Patients and society at large have a reasonable expectation that physicians will conduct themselves competently and in accordance with scientific evidence when rendering medical services, and physicians may find themselves liable to patients and foreseeable third parties if that duty is breached.

Health Benefits of Marijuana

Marijuana has no officially recognized health benefits according to the U.S. Food and Drug Administration ("FDA")[15] and more than twenty leading medical and scientific organizations.[16] Recent studies, however, have identified potential benefits from marijuana for treating a limited number of medical conditions, including chronic neuropathic or cancer pain, spasticity associated with neurological disorders like multiple sclerosis, nausea, appetite loss, and severe weight loss associated with wasting illnesses such as cancer and AIDS.[17] Comparable benefits are often achieved, however, from FDA-approved pharmaceutical medications that are synthesized from chemicals found in the marijuana plant (cannabinoids), which are not smoked and have far less or no intoxicating effects.[18]

Pursuant to the U.S. Controlled Substances Act,[19] the FDA and Drug Enforcement Administration ("DEA") work collaboratively to establish a drug's legal status. A drug that has no recognized medical benefit and a high potential for abuse or addiction is listed in Schedule I.[20] Drugs that are listed in Schedules II through V have recognized medical benefits and pose respectively less degrees of risk for abuse and other dangerous medical side effects.[21]

The FDA employs a highly rigorous review process in determining whether a drug has proven medical benefits and is safe and effective for medical use.[22] An applicant must first conduct preclinical testing on animals to demonstrate that the drug is safe for human testing. If it passes this minimum threshold, studies may then be conducted on healthy human volunteers to assess common side effects of the drug and determine how it is metabolized and excreted in humans. If there is no evidence of toxicity, preliminary efficacy studies are next conducted on patients having a relevant disease or condition to examine the drug's ability to treat that condition. To ensure that the findings are scientifically reliable, at least some of the studies must be concurrent controlled clinical trials, meaning that participants are assigned randomly or in an otherwise unbiased manner to receive either the experimental drug or a placebo (inactive) substance, a different medication, or another form of treatment such as counseling.[23]

If the results of the preliminary efficacy studies are favorable, the drug then moves on to large-scale effectiveness studies involving large numbers of

continued on page 4

continued from page 3

subjects (often in the hundreds) to examine its effects in different populations, at varying dosages, and in combination with other commonly used medications or treatments. Finally, an independent team of physicians, statisticians, toxicologists, pharmacologists, chemists and other scientists review all of the findings and approve the drug for sale if its proven benefits are determined to outweigh the known risks. Once approved, post-marketing surveillance continues to identify infrequent adverse reactions which may arise when the medication is administered in daily practice to large numbers of patients. If adverse reactions are identified, they are typically described in package inserts or box warnings which must accompany the medication and alert physicians to potential contraindications and warnings about its use.[24] In some instances, approved medications may be withdrawn from the market if it is determined that emerging risks outweigh the benefits that the medication may provide.[25]

Marijuana is presently listed as a Schedule I drug, reflecting the FDA's conclusion that it has no proven medical benefit and carries a high risk for abuse or addiction. As indicated on the FDA's website, "[t]he FDA has not approved any product containing or derived from botanical marijuana for any indication. This means that the FDA has not found any such product to be safe or effective for the treatment of any disease or condition."[26] The FDA has, however, approved two pharmaceutical cannabinoids, dronabinol and nabilone, which contain the primary psychoactive ingredient in marijuana, THC, and have relatively minimal intoxicating or addictive effects.[27] These medications are approved for the treatment of nausea and to increase appetite and weight gain in patients suffering from wasting illnesses associated with diseases like AIDS or cancer. Other countries, including the United Kingdom and Canada, have approved a third medication, nabiximols (Sativex), which contains THC and another non-intoxicating chemical found in marijuana, cannabidiol, which may offer benefits for treating neurological conditions such as childhood epilepsy.[28]

Importantly, an absence of FDA approval does not prove that marijuana is ineffective or unsafe. It simply means that the benefits and risks of the drug have not been studied sufficiently to meet FDA standards, and the risk/benefit ratio is therefore undetermined. Because marijuana is a Schedule I drug, researchers have had a very difficult time studying its effects.[29] Researchers must first obtain a license from the DEA and have the study approved by the FDA. In addition, they must generally obtain research-grade marijuana (marijuana of a proven potency that has no impurities) through the National Institute on Drug Abuse ("NIDA"). NIDA provides research-grade marijuana for studies that have received funding from the National Institutes of Health ("NIH"), or for non-NIH-funded projects that have an approved Investigational New Drug ("IND") application on file with the FDA and have been approved as scientifically valid by a Department of Health and Human Services ("HHS") scientific review panel. Since 1970, the University of Mississippi has been the only facility approved by the DEA to grow and harvest marijuana for NIDA-sponsored studies; however, the DEA recently announced that it will allow additional growers to apply for a registration to produce and distribute marijuana for research purposes.[30]

These manifold obstacles have led several leading scientific and practitioner organizations to call for the FDA to reclassify marijuana from Schedule I to a less restrictive schedule to permit freer research into its potential medicinal benefits.[31] Yet, in August 2016 the DEA denied a petition to reclassify marijuana from Schedule I based on an exhaustive review of the scientific literature conducted by HHS.[32] The DEA and HHS concluded that there is no statutorily authorized basis to reschedule marijuana because "marijuana has a high potential for abuse, has no accepted medical use in the United States, and lacks an acceptable level of safety for use even under medical supervision."[33] Nevertheless, the DEA indicated a willingness to ease restrictions on research into the potential medical benefits of marijuana, including, as mentioned, permitting additional growers to produce research-grade marijuana for federally funded studies.[34]

Despite substantial hurdles to conducting good-quality research, recent studies have identified potential health benefits from marijuana for treating a limited number of medical conditions. The quality of these studies does not come close to satisfying FDA standards for effectiveness; nevertheless, they provide sufficient promise or "proof of concept" to justify conducting additional research. Systematic reviews performed by leading medical researchers have concluded there is high-quality evidence suggesting that marijuana may be beneficial for treating chronic neuropathic or cancer pain, and for ameliorating spasticity associated with certain neurological disorders such as multiple sclerosis.[35] However, comparable benefits may be achieved from nonintoxicating and nonaddictive pharmaceutical cannabinoids.[36] Moreover, while there is also considerable evidence that marijuana increases appetite and reduces nausea for persons suffering from wasting illnesses, the effects appear to be no better than for medications already approved by the FDA for treating these conditions.[37] Where there is comparable evidence of effectiveness for both marijuana and an FDA-approved pharmaceutical cannabinoid, leading medical experts advise physicians to

begin treatment with the cannabinoid because an acceptable risk/benefit profile has been established for that medication, and switch to marijuana if the cannabinoid proves ineffective.[38]

Although anecdotal testimonials abound from some patients and physicians, to date there is insufficient evidence to conclude whether marijuana or cannabidiol is effective for treating childhood epilepsy, movement disorders such as Parkinson's or Tourette's syndrome, glaucoma, or urinary tract disorders.[39] Moreover, any assertions that marijuana or pharmaceutical cannabinoids can treat other medical conditions, such as mental health disorders, substance use disorders, Alzheimer's disease, autism, insomnia or autoimmune disorders are speculative at this juncture.[40] In fact, as will be discussed further, evidence suggests that marijuana is likely to worsen the prognosis for many mental health and substance use disorders and interfere with the effects of proven treatments for these conditions.[41]

Recommending the use of a non-FDA-approved substance is not necessarily evidence of malpractice. Physicians frequently recommend alternative therapies to their patients, including herbal plants and extracts.[42] The Dietary Supplement Health and Education Act of 1994[43] classifies most herbal plants as dietary supplements, which can be produced, sold and marketed without demonstrating their safety or efficacy. The FDA bears the regulatory burden of proving that a dietary supplement is unsafe before it can be removed from the market.[44] The opposite burden of proof applies to pharmaceutical medications, which must be proven safe and effective before they can be marketed or sold.[45]

Physicians also frequently prescribe FDA-approved medications for conditions or disorders that are not approved by the FDA.[46] For example, a medication might be approved for the treatment of epilepsy but physicians might prescribe it to treat migraine headaches, sleep disorders, or depression. Once a medication has been approved by the FDA for a specified use, physicians are generally free to prescribe it for other off-label uses if, in their professional judgment, it is likely to be safe and effective for those conditions.[47] In many instances, off-label use is based on anecdotal impressions or clinical observations rather than on scientific evidence of safety and effectiveness.[48]

The terms innovative therapy, alternative medicine, complementary medicine or unorthodox medicine are commonly used to describe non-FDA-approved treatments lacking scientific evidence of effectiveness, and may also refer to off-label uses of FDA-approved medications that have not been evaluated.[49] Although patients do not have a fundamental right to bypass the FDA review process for pharmaceutical medications,[50] courts will generally recognize a patient's right to seek unorthodox homeopathic remedies, naturopathic treatments, faith-healing practices, and off-label uses of approved medications.[51] Providing or recommending such alternative treatments typically heightens the physician's duty to inform the patient about the limited scientific basis for the treatment, any known risks of the treatment, the possibility of unknown or unstudied risks, and the availability of FDA-approved treatments, if any, that are proven to be effective for the same condition.[52]

Health Risks of Marijuana

Although the potential health benefits of marijuana have not been studied nearly sufficiently, a wide range of health risks has been reliably identified. Every intoxicating substance has a dependence liability, defined as the statistical probability that a person who uses that substance will develop a compulsive addiction. The dependence liability for marijuana is approximately nine percent for adult users, 17 percent if use begins during adolescence (which it often does), and nearly 40 percent for persons who use marijuana several times per week.[53] A hallmark symptom of substance dependence is uncomfortable or painful withdrawal symptoms when levels of the substance decline in the bloodstream. When marijuana-dependent individuals stop taking marijuana, they experience a withdrawal syndrome comparable to that of nicotine.[54] Cannabis dependence has been an officially recognized psychiatric diagnosis since 1980,[55] and cannabis withdrawal syndrome is now recognized, as well.[56]

Chronic marijuana use is reliably associated with apathy or reduced motivation to engage in goal-directed behaviors, a syndrome referred to as an amotivational state.[57] Neuroimaging studies suggest this may occur, in part, because marijuana blunts transmission of or sensitivity to the neurotransmitter dopamine in brain regions which are responsible for reward-based learning, thus reducing motivation to accomplish intellectual tasks.[58] Researchers have not ruled out the possibility that impaired motivation may lead to marijuana use rather than the other way around. Unmotivated people may simply be more inclined to use marijuana. Nevertheless, if marijuana were an FDA-approved medication, such a strong and consistent correlation with a serious adverse syndrome would be more than sufficient to require a package insert alerting physicians to the potential medical risk.[59]

Even when chronic marijuana users are not intoxicated, they perform significantly worse than nonusers on neuropsychological tests of cognitive functioning, including attention, learning, memory, motor skills, and verbal abilities.[60] Faced with novel or complex intellectual tasks, their decision-making processes tend to be more impulsive, irrational, and ineffective than those of nonusers.[61] Some evidence suggests that these deficits may improve after at least 30 consecutive days of abstinence.[62] However, when use begins in adolescence, the effects

continued on page 6

continued from page 5

are far more likely to be long-lasting or permanent. Repetitive use of marijuana during the teen years is associated with a six- to eight-point decline in Intelligence Quotient ("IQ").[63] This impairment in intelligence appears to be global, meaning that deficits are found in a wide range of areas, including verbal intelligence, memory, processing speed, perceptual reasoning, visual perception, manual dexterity, psychomotor speed, and executive functioning (planning, judgment, and insight).[64] Lower IQ scores among adolescent-onset marijuana users have been measured for at least a full year after complete cessation of usage,[65] poorer physical and mental health outcomes have been measured for at least nine years,[66] reduced occupational productivity has been measured for at least 17 years,[67] lesser quality of life has been measured for 21 years,[68] and greater odds of physical or mental disability have been measured for 39 years.[69]

These serious cognitive and adaptive impairments occur primarily in adolescent-onset or young-adult-onset marijuana users, and medical marijuana laws typically exclude or curtail access for teens to medical marijuana. Yet, whenever marijuana has been decriminalized for medical or recreational purposes, the largest upsurge in use has typically been among teens and young adults,[70] the persons most susceptible to long-term brain impairment. As large numbers of older adults now also use marijuana—often for the first time or after decades of nonuse—in response to medical marijuana laws, it is unknown what cognitive impairments may ensue for these marijuana-inexperienced individuals whose brain functioning may already be compromised by incipient dementia or normal aging.[71]

Even when used sporadically, marijuana can cause lasting structural or neurochemical changes in the human brain. Recent studies employing advanced brain-imaging techniques have uncovered specific brain regions in which some of these changes are occurring. Scientists have discovered structural abnormalities among occasional marijuana users in the nucleus accumbens and amygdala (responsible, in part, for emotional regulation and learning from experience),[72] the prefrontal cortex (responsible for planning, judgment, and inhibition of risky behaviors),[73] and the limbic striatum (responsible for motivation and attention).[74] Again, scientists have not disentangled cause and effect. Preexisting neurological impairments may predispose some individuals to use marijuana. Nevertheless, in the face of such persistent and powerful correlations with serious adverse syndromes, the FDA would almost certainly require a package insert if marijuana were an approved pharmaceutical medication.

The cognitive effects of marijuana have important implications for risky and impaired driving. Occasional use of marijuana by non-addicted individuals increases the odds of becoming involved in a car accident by more than two fold.[75] In laboratory simulation studies, single-dose administration of marijuana significantly increased lane weaving, impaired subjects' ability to visually track other cars, reduced subjects' reaction times, and interfered with their ability to divide their attention (e.g., drive and change the radio station at the same time).[76] Among chronic marijuana users, these impairments have been found to last for at least three weeks following complete abstinence, when the subjects were no longer experiencing the intoxicating effects of the drug.[77] Individuals may believe wrongly that they are capable of driving when, in fact, they are dangerously impaired. In Colorado, traffic fatalities involving marijuana roughly doubled in the first two years after marijuana was legalized, and marijuana caught up with alcohol as the leading cause of traffic accidents.[78]

Longitudinal studies show a consistent association between adolescent-onset marijuana use and subsequent development of severe psychotic disorders, including schizophrenia.[79] Scientists have recently identified specific genes or gene-clusters (genotypes) that are activated or inhibited by marijuana use, and which significantly increase the risk of developing a severe psychotic disorder such as schizophrenia.[80] Following an initial psychotic episode, continued use of marijuana is also associated with a significantly poorer prognosis, including more hospital readmissions, more days spent in the hospital, and a greater likelihood of being involuntarily committed for treatment.[81]

Increased rates of other mental health disorders are also known to co-occur with marijuana use, including major depression, bipolar disorder (manic-depression), and post-traumatic stress disorder ("PTSD").[82] However, it is unclear which disorder, if any, is responsible for this co-morbidity. Some mentally ill individuals may use marijuana as an effort to self-medicate psychiatric symptoms, or perhaps marijuana may trigger a latent genetic predisposition to mental illness. By following participants prospectively for several years, researchers have determined that the onset of mental illness typically occurs after marijuana use,[83] which would appear to be inconsistent with a self-medication hypothesis. However, a recent national longitudinal study in the United States found no correlation after three years between marijuana use and subsequent rates of mood or anxiety disorders.[84] Perhaps three years is too soon for mental illness to manifest, or perhaps the relationship between mental illness and marijuana

use is more complicated than expected. For example, mental illness and marijuana use may emerge independently from a common genetic vulnerability, which would be difficult to detect in a longitudinal study. Additional neuroimaging and genetic studies are needed to better understand the comorbid relationship between marijuana use and serious mental illness.

Marijuana use is strongly linked to subsequently higher rates of dependence on alcohol and other drugs,[85] general psychological distress[86] and suicidality[87] after follow-up periods of three to eight years. For individuals who are dependent on other substances of abuse, such as heroin, alcohol or cocaine, use of marijuana is reliably associated with significantly higher rates of treatment failure and relapse to these other substances.[88]

Smoking marijuana also causes many of the same respiratory and cardiac symptoms as tobacco, including frequent lung illnesses, a higher risk of lung infection, daily cough, and increased phlegm.[89] Marijuana use raises heart rate for up to three hours, which can increase the chance of a heart attack or dangerous cardiac event.[90] Marijuana smoke contains 50 percent more carcinogens than tobacco smoke;[91] however, it is unknown whether marijuana smokers have a higher risk for lung cancer.[92] Marijuana use during pregnancy or lactation is linked to an increased risk of brain and behavioral problems in babies and young children.[93] Finally, weekly use of marijuana is associated with a significantly lower sperm count and sperm concentration in young adult males.[94]

Malpractice Liability for Medical Marijuana

As stated earlier, no published court opinion was found that has considered potential malpractice liability for a physician certifying or recommending medical marijuana. Courts may, however, be expected to confront such cases in light of the fact that states are rapidly broadening patient access to medical marijuana, most expert organizations oppose these measures on scientific grounds, studies are increasingly uncovering serious health risks associated with its use, evidence is lacking or equivocal concerning its effectiveness for many health conditions, and less risky FDA-approved pharmaceutical cannabinoids are already available for the few conditions that marijuana may treat effectively. Presumably courts will analyze such cases by applying or adapting traditional medical malpractice principles to the new policy and scientific landscapes.

Duty of Care

The first issue courts will need to address in these cases is whether certifying the need for medical marijuana creates a traditional doctor/patient relationship, which carries with it a concomitant duty to render competent professional care.[95] The existence of a doctor/patient relationship does not turn on the question of whether a physician has prescribed an FDA-approved treatment. Rather, a professional duty of care is created by the virtue of the powers and authority vested in physicians through state licensure and accreditation laws, as well as the reasonable expectations of patients.[96] If a patient is legally obligated to obtain certification for medical marijuana from a physician, and if the patient reasonably believes that the physician will exercise professional judgment and training in making that decision, then a doctor/patient relationship is likely to be recognized. Courts typically find that a doctor/patient relationship has been created where the physician assumed some degree of responsibility for making a diagnostic or treatment decision, or saw the patient as part of a formal consultation even if the physician had no further involvement with the patient's care.[97]

Breach of Duty

A more complicated issue is determining whether a physician has breached the duty of care by engaging in substandard medical practice. For example, a question might arise as to whether a physician breached the duty of care by failing to take an adequate medical history of a patient which would have uncovered contraindicated conditions that are likely to be made worse by marijuana use, such as psychosis, addiction or respiratory disease. Similarly, a physician might be found to have breached the duty of care by certifying marijuana to treat a condition that is unlikely to improve from its use, such as autism or anxiety. In such cases, the potential medical risks associated with marijuana use might not be justified by any known or reasonably anticipated benefits that are likely to ensue.

Some states employ a custom-based test for determining the standard of care, requiring the physician to provide the type and level of care that an ordinary and prudent physician with comparable training and experience would have provided under similar circumstances in the same or a similar locality.[98] Expert testimony from physicians who are familiar with the relevant locality and area of practice is usually required to establish the customary standard of care.[99] Notably, in jurisdictions following a custom-based standard, medical experts are not required to describe, or even to consult, scientific studies to support their conclusions. The critical question is not whether the physician's actions were scientifically valid, but rather whether they were performed in accordance with customary medical practices in the relevant locality and area of specialization.[100]

In contrast to a custom-based test, a growing number of jurisdictions apply a reasonable physician standard, which evaluates the physician's actions against what he or she should have done as opposed to what is customarily done.[101] In these jurisdictions, scientific evidence supporting or refuting a given practice is directly on point to the question of whether the physician's

continued on page 8

continued from page 7

treatment was reasonable and competent.[102] On direct examination, expert witnesses may describe the results of scientific studies to support their conclusions about reasonable care, or on cross-examination may be called upon to defend their conclusions in the face of conflicting findings. For example, if a physician certified the use of medical marijuana for a patient with an anxiety disorder and a serious history of respiratory illness, a medical expert witness might testify that studies have found no evidence of medical benefits from marijuana for the treatment of anxiety, and have identified health risks for patients with anxiety and respiratory disease.

Several nationally recognized scientific and practitioner organizations have published official position statements against medical marijuana.[103] Given the current state of scientific knowledge, these organizations have concluded that the risk/benefit ratio for medical marijuana is unknown or does not justify its use to treat any recognized medical condition. Defendants in states applying a reasonable physician standard may face substantial uphill battles defending their actions in the light of these expert position statements.

Traditionally, documents such as these were inadmissible as hearsay to prove the truth of the matter asserted, but in some instances could be used on cross-examination to impeach or discredit a witness.[104] The more modern approach adopted by many states is to admit such evidence on direct or cross examination if the expert acknowledges that the source is reliable and authoritative, or if the court takes judicial notice of its reliability.[105] Regardless of what evidentiary standard is applied, lawyers with a modicum of ingenuity can often get this evidence admitted to impeach or resurrect testimony concerning the appropriate standard of care. In jurisdictions that apply a reasonable physician standard, physicians who certify marijuana for medicinal use may find themselves having to explain away contradictory scientific advisories from a plethora of leading national organizations.

Notably, a small number of professional organizations have issued position statements in favor of medical marijuana,[106] and as discussed earlier scientific studies do lend support for its use in treating a limited number of medical conditions, including nausea, appetite loss, neuropathic pain, and spasticity associated with multiple sclerosis.[107] This evidence may be admissible to argue that there are two schools of thought concerning the use of marijuana for some medical conditions. The existence of two schools of thought generally serves as a conclusive defense against a medical malpractice claim.[108] Courts are reluctant to wade into disputes between opposing factions of the medical community because judges and lawyers are not qualified by knowledge or training to weigh the scientific bases of conflicting medical theories.[109] Many jurisdictions require a considerable number of recognized and reputable physicians to support a practice in order to establish a second school of thought.[110] In these jurisdictions, physicians are more likely to prevail if they certify the use of marijuana for conditions like chronic pain or spasticity, for which there is some evidence of efficacy and support from at least some professional organizations. However, success is less likely for other conditions, such as anxiety or depression, for which there is little or no evidence of effectiveness and reputable professional support is largely absent.

A few jurisdictions, however, lend an expansive interpretation to the two schools of thought doctrine. These jurisdictions give substantially greater weight to divided medical opinion, and look more favorably on a physician's actions if there is any reasonable difference of opinion among experts.[111] In these jurisdictions, a defense based on two schools of thought may also succeed for conditions such as anxiety, for which treatment with marijuana receives small pockets of support in the medical community.

Professional Practice Guidelines

State laws vary considerably in terms of the educational and professional obligations they place on physicians concerning the use of medical marijuana. As noted above, many states require physicians to receive several hours of continuing education, examine each patient personally, obtain informed consent for treatment, develop a treatment plan, review the patient's progress, and maintain accurate medical records.[112] These statutes establish a floor of acceptable practices, and failing to abide by the basic requirements may lead to professional disciplinary action, malpractice exposure, and potentially to criminal prosecution.

Professional organizations and leading medical experts have gone considerably further in proposing higher standards of practice for medical marijuana. Beyond the basic obligations imposed by many state statutes, experts have, for example, recommended that physicians have a preexisting and ongoing treatment relationship with each patient, as opposed to acting merely as a consultant; schedule routine follow-up visits with every patient; explicitly rule out the presence of contraindicated co-occurring conditions, including substance use disorders, major depressive disorder, anxiety disorders, and respiratory tract infections; begin treating patients with FDA-approved and evidence-based treatments, including pharmaceutical cannabinoids, before resorting to marijuana if those treatments fail; ensure that the physician has adequate information concerning

the specific dosage and composition of the marijuana product; and ensure that the physician is well-trained in addiction medicine and prepared to make immediate and appropriate referrals for substance use disorder treatment where indicated.[113]

In states that apply a reasonable physician standard, these practice guidelines might be admissible to show that a physician's conduct fell short of the appropriate standard of care, or to rebut or impeach a physician's assertion that he or she exercised due care in treating the patient.[114] Whether courts will hold physicians accountable merely for complying with the basic conditions enumerated in medical marijuana statutes or whether they will raise the bar in the light of published practice guidelines is an open question. In the interests of "defensive medicine," physicians and their attorneys are advised to familiarize themselves with the practice guidelines promulgated by leading medical organizations and experts, and conform their practices accordingly. Needing to justify why one's actions fell short of recommended standards of care published by leading scientific and practitioner organizations is unlikely to sit well with a judge or jury. Worse, not being aware of the existence of these guidelines could be viewed quite negatively in a medical malpractice action.

Informed Consent and Assumption of the Risk

Patients generally have a right to forego accepted medical treatments and seek innovative or unorthodox therapies so long as they knowingly, intelligently and voluntarily assume the risk for that decision.[115] Patients may not, however, waive a physician's duty to render competent professional care or adhere to professional practice guidelines and statutory provisions.[116] Because these duties are imposed by law or reflect the medical profession's legitimate role in policing the conduct of its own members, patients have no standing or authority to relieve a physician of the obligations. A patient may not, for example, waive a physician's duty to perform a thorough diagnostic assessment or take a detailed medical history before certifying or recommending the use of marijuana. Assuming a physician has performed a competent diagnostic assessment and reached an educated conclusion about potentially effective courses of action, it is the patient's prerogative to choose from among the promising alternatives.

Material Information

Except in limited circumstances such as medical emergencies, physicians are generally required to provide their patients with any material information that is likely to bear on the decision whether to choose or forego a medical treatment, including the likelihood and magnitude of foreseeable risks from the treatment, the likelihood and magnitude of anticipated benefits, and the relative odds of success compared with alternative treatments that may be available for the same condition.[117] Some states employ a patient-based test for assessing materiality, requiring physicians to provide information that an ordinary, reasonable and prudent patient would want to know in making the decision.[118] In these states, the factfinder (judge or jury) typically decides whether disclosure was adequate. Other states employ a custom-based test, requiring physicians to provide information that physicians practicing in the same or a similar locality and area of practice would ordinarily provide.[119] In those states, expert medical testimony is typically required to define the customary standard for disclosure.

Studies indicate that numerous factors influence a patient's decision to seek alternative and complementary treatments, including lifestyle preferences and cultural beliefs. Chief among these factors is the perceived efficacy of the treatment in improving the patient's condition.[120] Patients also frequently harbor false beliefs that herbal remedies are harmless when, in fact, many carry serious risks for adverse health effects and dangerous interactions with prescription medications.[121] Therefore, material elements of informed consent should always include, at a minimum, a frank discussion with the patient about the proven and unproven health risks and benefits of marijuana, the known risk/benefit ratio, the possibility of unknown or unstudied risks, the availability of effective FDA-approved medications for the patient's condition, the possibility of dangerous interactions with other medications the patient might be taking, and the possibility that the product may contain contaminants resulting from inadequate quality control over the manufacturing process.[122] It is ordinarily insufficient to deliver this information in a general consent form. Information must be provided concerning the specific treatment under consideration, the patient's specific medical condition, and the known risks and benefits of alternative treatments for that same condition.[123]

Causality

Plaintiffs must also make a showing of causality, meaning not only that some harm was caused by ingesting medical marijuana but also that the patient would most likely not have used it if adequate disclosure had been made. Most states apply an objective test for causality, requiring a finding that an ordinary, reasonable and prudent patient would not have undergone the treatment if the potential harms had been disclosed.[124] Other states apply a subjective test, requiring the factfinder to conclude that the plaintiff in the instant case would not have undergone the treatment.[125] Whichever causality test is applied, the weight of national scientific opinion will usually bear directly on the question of whether the plaintiff or a reasonably prudent patient would have elected to proceed with a treatment in light of the known medical risks and benefits.[126] Plaintiffs can

continued on page 10

continued from page 9

often make a strong case that the results of scientific studies, professional practice guidelines, and position statements issued by national organizations are material information that, if known, would have led them to choose a different course of action.

Physicians are not required to provide information that is widely known by the public or already known to the patient.[127] For example, the intoxicating effects of marijuana are widely known; therefore, physicians are probably not obliged to describe these effects. Many patients, however, are unlikely to be aware that impairments in cognitive and motor functioning can last for nearly a month after cessation of usage.[128] Therefore, patients should be advised not to drive a car, operate heavy machinery, or perform other potentially hazardous tasks for at least several hours after cessation of use,[129] and perhaps for up to one month for chronic users or those who have a low physiological tolerance to the drug. Many patients also believe that marijuana is beneficial for treating conditions such as anxiety, depression, PTSD, autism, addiction, glaucoma, and autoimmune disorders, when in fact it is likely to exacerbate these conditions and interfere with the benefits of effective treatments.[130] Physicians may be obliged, therefore, to affirmatively disabuse patients of such generally held and erroneous beliefs.[131] For these reasons, several leading practitioner organizations and national experts have proposed augmenting the informed consent requirements for medical marijuana to include telling patients that marijuana is not FDA-approved, has little or no support from leading medical and scientific organizations, has not been shown to be effective for treating most medical conditions for which it has been studied, is not a standardized or purified product, and can precipitate relapse for persons with mental health and substance use disorders.[132] Whether courts will assign weight to these augmented expert disclosure recommendations remains an open question.

Failing to obtain adequate informed consent from patients may also expose physicians to third-party liability for foreseeable harms to other persons.[133] For example, physicians could be held liable to third parties who are injured in a car or work accident caused by a patient's use of medical marijuana. Although the physician has no doctor/patient relationship with such third parties, he or she may be liable in ordinary negligence for nonfeasance by failing to take simple precautions that could have avoided a foreseeable and serious injury. Courts have found physicians liable to third parties, for example, for failing to warn patients about potential driving hazards associated with the use of prescription medications.[134]

Warning a patient about such risks is ordinarily sufficient to shield the physician from third-party liability even if the patient ignores the physician's advice and engages in hazardous activity. Courts will typically view a patient's willful noncompliance with a physician's directive as an intervening factor that breaks the legal chain of causation.[135] Once a physician has duly warned a patient about the known and reasonably anticipated risks of a medication, it becomes the patient's responsibility to act accordingly and with due caution.

Conclusion

Policy makers often make decisions based on the majority will of the electorate, but physicians and other healthcare practitioners do not. Authorizing physicians to certify or recommend medical marijuana does not, in any way, absolve them from rendering competent and scientifically informed medical care. Physicians who wade into the terrain of medical marijuana must understand that although their actions may not be criminally culpable in legalizing states, they are nonetheless recommending or certifying a non-FDA-approved treatment that is not supported or recognized by the large majority of their professional colleagues. Doing so may expose them to malpractice liability no differently than if they prescribed any other potentially hazardous and scientifically controversial experimental treatment.

It is important, therefore, for physicians and health lawyers to familiarize themselves with the scientific evidence and applicable legal doctrines in their jurisdictions pertaining to medical marijuana. Physicians practicing in jurisdictions that apply a custom-based standard of care, or that construe the two schools of thought doctrine expansively to encompass any reasonable division of medical opinion, might take solace in the fact that medical marijuana receives pockets of support from certain sectors of the medical community. However, those practicing in states that apply a reasonable physician standard, or that require a substantial minority of opinion to establish an alternative school of thought, may find themselves pitted in court against the national weight of scientific opinion and the pillars of mainstream medicine. This is especially so if they recommend or certify marijuana for unproven or currently discredited purposes, such as to treat anxiety or depression.

Physicians are further advised to take informed consent procedures very seriously in these cases. Meticulous efforts are called for to educate patients about what is known and not known about marijuana, and to disabuse patients of any misconceptions they may have stemming from public advocacy campaigns that often overstate the proven health benefits of marijuana and understate the known

risks. Patients have a reasonable expectation that physicians, as learned professionals, will conduct themselves impartially and competently in rendering medical treatment, and the law may compensate them and foreseeably injured third parties if that duty of care is breached.

The author gratefully acknowledges the intellectual contributions of Beth Ann Middlebrook, Esq., and Hon. Louis J. Presenza (ret.) for sharing their expert knowledge concerning medical marijuana and providing invaluable feedback on earlier versions of this article. The views expressed in this article are solely those of the author and do not necessarily represent the opinions or positions of any individuals or organizations with which he is affiliated.

Douglas B. Marlowe, is Chief of Science, Law & Policy for the National Association of Drug Court Professionals. He earned a bachelor's degree in psychology from Brandeis University, a law degree from Villanova University, and a Ph.D. in clinical psychology from Hahnemann University. He completed an internship in clinical psychology and a fellowship in neuropsychology at the Albert Einstein College of Medicine and Montefiore Medical Center.

Dr. Marlowe's research and practice focus on the effects of drug courts and other rehabilitation programs for persons with substance use disorders involved in the justice system. He is a Fellow in addiction psychology, psychopharmacology and substance abuse from the American Psychological Association ("APA"), and has received proficiency certification in the treatment of psychoactive substance use disorders from the APA College of Professional Psychology. Dr. Marlowe has published over 150 articles, monographs, books, and book chapters on the topics of forensic psychology, correctional rehabilitation, and treatment of substance use disorders. He can be reached at *dmarlowe@nadcp.org*.

Endnotes

1 Delta-9-tetrahydrocannabinol or THC is the primary psychoactive ingredient in marijuana that causes intoxication.

2 *See* ProCon.org, 25 Legal Medical Marijuana States and DC: Laws, Fees, and Possession Limits (last updated 6/28/2016), *at* http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881; ProCon.org, 16 States With Laws Specifically About Legal Cannabidiol (CBD) (last updated 3/17/2016), *at* http://medicalmarijuana.procon.org/view.resource.php?resourceID=006473; *see also* Jane C. Maxwell & Bruce Mendelson, *What Do We Know Now About the Impact of the Laws Related to Marijuana?*, 10 J. ADDICTION MED. 3, 5 Fig. 2 (2016) (reporting that 11 states had bills pending during the 2015 legislative session to broaden patient access to medical marijuana).

3 *See* Pew Research Center, Public Support for Legalizing Medical Marijuana 1 (2010) (finding that 73% of Americans support legalizing marijuana if authorized by a doctor), *at* http://people-press.org/2010/04/01/public-support-for-legalizing-medical-marijuana/; Pew Research Center, In Debate Over Legalizing Marijuana, Disagreement Over Drug's Dangers 4 (2015) (finding the primary reason for supporting legalization of marijuana is its perceived medicinal benefits), *at* http://people-press.org/2015/04/14/in-debate-over-legalizing-marijuana-disagreement-over-drugs-dangers/; *see also* Pew Research Center, View of Marijuana – Legalization, Decriminalization, Concerns 1 (2014) (finding that 54% of Americans favor legalizing marijuana for recreational purposes), *at* http://people-press.org/2014/04/02/section-2-views-of-marijuana-legalization-decriminalization-concerns/; Sharon R. Sznitman & Anne L. Bretteville-Jensen, *Public Opinion and Medical Cannabis Policies: Examining the Role of Underlying Beliefs and National Medical Cannabis Policies*, 12 HARM REDUCTION J. 46 (2015) (finding that 78% of Israeli citizens and 53% of Norwegians support medical marijuana).

4 For a discussion of national organizations taking positions against medical marijuana, see *infra* note 16 and accompanying text.

5 For a discussion of negative health consequences associated with marijuana use, see *infra* notes 53 to 94 and accompanying text.

6 For a discussion of the proven health benefits of marijuana, see *infra* notes 35 to 40 and accompanying text.

7 *See infra* notes 95 to 97 and accompanying text.

8 *See* Findlaw, Medical Marijuana Laws by State (2016) (listing covered medical conditions by state in medical marijuana laws), *at* http://healthcare.findlaw.com/patient-rights/medical-marijuana-laws-by-state.html; Esther K. Choo & Sherry L. Emery, *Clearing the Haze: The Complexities and Challenges of Research on State Marijuana Laws*, ANNALS N.Y. ACAD. SCI. 3 (2016) (noting that covered medical conditions vary from a few specific conditions to 45 conditions, and may include open-ended language permitting latitude in treating a wide range of debilitating symptoms), *available at* doi: 10.1111/nyas.13093; Jessica Bestrashniy & Ken C. Winters, *Variability in Medical Marijuana Laws in the United States*, 29 PSYCHOL. ADDICTIVE BEHAV. 639, 640 tbl. 1 (2015) (reporting numbers of covered medical conditions by state in medical marijuana laws).

9 *See, e.g.*, California Dept. of Public Health, Medical Marijuana Identification Card Program, Physician Responsibilities (2016), *at* https://cdph.ca.gov/programs/Pages/MMPDrRespon.aspx; Massachusetts Department of Public Health, Bureau of Health Care Safety and Quality, Medical Use of Marijuana Program, Guidance for Physicians Regarding the Medical Use of Marijuana (as amended June 9, 2015), *at* http://mass.gov/eohhs/docs/dph/quality/medical-marijuana/physician-guidance-2015-06-09.pdf.

10 *See, e.g.*, Massachusetts Medical Society, Massachusetts Medical Marijuana Law: Considerations for Physicians 3 (2013) (noting that physician disciplinary processes applicable to medical marijuana are well established by the Board of Medicine, and the Dept. of Public Health reserves the right to revoke a registration to certify medical marijuana if a physician commits fraud or fails to meet continuing education requirements), *at* http://massmed.org/Advocacy/Key-Issues/Medical-Marijuana/Massachusetts-Medical-Marijuana-Law--Considerations-for-Physicians/#.V5aAt7grKUk; Massachusetts Medical Society, Overview of Physician Sections of Medical Marijuana Regulations (2013) (listing grounds for revoking a physician's registration for medical marijuana), *at* http://massmed.org/Advocacy/Key-Issues/Medical-Marijuana/Overview-of-Physician-Sections-of-Medical-Marijuana-Regulations/#.V5aDSLgrKUk.

11 *See Colorado v. Montante*, Co. Ct. App. No. 13CA1858 (Co. Ct. App. 2015) (affirming convictions for fraud and attempting to influence a public servant for a physician who misrepresented a patient's need for medical marijuana), *available at* http://cases.justia.com/colorado/court-of-appeals/2015-13ca1858.pdf?ts=1428591942; *but see Arizona v. Gear*, No. CR-14-0408-PR (Az., May 6, 2016) (holding that Arizona's medical marijuana statute shields physicians from criminal prosecution for failing to follow the requirements of the law), *available at* https://azag.gov/sites/default/files/State_of_AZ_VS_Gear.PDF.pdf.

12 *See* BLACK'S LAW DICTIONARY 847 (7th ed., 2000) (defining negligence per se); Law and Physician Health Law Web Site, Negligence per se (1993), *at* http://biotech.law.lsu.edu/Books/lbb/x133.htm.

13 See *infra* notes 98 to 114 and accompanying text.

14 *See* Timothy Caulfield & Colin Feasby, *Potions, Promises and Paradoxes: Complementary and Alternative Medicine and Malpractice Law in Canada*, 9 HEALTH L. J. 183, 193-3 (2001) (noting that nearly one quarter of patients using homeopathic and herbal remedies have experienced serious adverse side effects, occasionally leading to product liability actions).

15 *See* U.S. Food and Drug Administration, FDA and Marijuana 1 (2016) (indicating the FDA has not approved marijuana as safe and effective for any medical use), *at* http://fda.gov/newsevents/publichealthfocus/ucm421163.htm.

16 *See* ALISON MACK & JANET JOY, MARIJUANA

continued on page 12

continued from page 11

AS MEDICINE? THE SCIENCE BEYOND THE CONTROVERSY 6 (Nat'l Acad. Sci., 2001) (reporting that the National Academy of Sciences' Institute of Medicine found little reason to recommend crude marijuana as medicine, particularly when smoked), *available at* file:///C:/Users/Owner/Downloads/9586.pdf; American Academy of Addiction Psychiatry, Position Statement on Medical Marijuana 1 (2015) (concluding that the known risks of marijuana are not outweighed by any scientific demonstration of benefits), *available at* http://aaap.org/wp-content/uploads/2016/02/HC-MMJ-position-statement-Jan-2016-rw.pdf; American Academy of Family Physicians, Medical Use of Marijuana 1 (2016) (concluding that the use of marijuana is not based on high quality, patient-centered, evidence-based research), *available at* http://aafp.org/about/policies/all/marijuana.html; American Academy of Neurology, Position Statement: Use of Medical Marijuana for Neurological Disorders 1 (n.d.) (concluding there is insufficient evidence to make definitive conclusions concerning the effectiveness of marijuana or marijuana-based products for neurologic conditions), *available at* https://aan.com/uploadedFiles/Website_Library_Assets/Documents/6.Public_Policy/1.Stay_Informed/2.Position_Statements/3.PDFs_of_all_Position_Statements/Final%20Medical%20Marijuana%20Position%20Statement.pdf; American Academy of Pediatrics, American Academy of Pediatrics Reaffirms Opposition to Legalizing Marijuana for Recreational or Medical Use 2 (2015) (concluding that more research is needed to determine the efficacy and correct dosing for marijuana and cannabinoids), *available at* https://aap.org/en-us/about-the-aap/aap-press-room/pages/American-Academy-of-Pediatrics-Reaffirms-Opposition-to-Legalizing-Marijuana-for-Recreational-or-Medical-Use.aspx?nfstatus=401&nftoken=00000000-0000-0000-0000-000000000000&nfstatusdescription=ERROR:+No+local+token; American College of Obstetricians and Gynecologists, Marijuana Use During Pregnancy and Lactation 3 (2015) (recommending that obstetricians and gynecologists discourage patients from using marijuana during preconception, pregnancy and lactation), *available at* http://acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Marijuana-Use-During-Pregnancy-and-Lactation; American College of Physicians, Position Paper Supporting Research into the Therapeutic Role of Marijuana 1 (2008) (concluding that insufficient information is available concerning the indications of marijuana for conditions other than nausea, vomiting and weight loss), *available at* https://acponline.org/acp_policy/policies/supporting_medmarijuana_2008.pdf; American Epilepsy Society, AES Position on Medical Marijuana 1 (2014) (concluding that only anecdotal reports support the use of marijuana for treating epilepsy), *available at* https://aesnet.org/sites/default/files/file_attach/AboutAES/PositionStatements/AES%20Position%20on%20Medical%20Marijuana.pdf; American Medical Association, Cannabis for Medicinal Use 1 (Resolution No. H-95.952, 2016) (clarifying that the AMA does not support state medical marijuana programs or endorse scientific evidence for the therapeutic use of marijuana), *available at* http://medicalmarijuana.procon.org/sourcefiles/AMA09policy.pdf; American Osteopathic Academy of Addiction Psychiatry, Position Paper on "Medical Marijuana" 1 (2011) (concluding that additional research is needed to clarify the therapeutic properties of marijuana), *available at* http://c.ymcdn.com/sites/www.aoaam.org/resource/resmgr/Docs/Medical_Marijuana_(AOAAM).pdf; American Psychiatric Association, Position Statement on Marijuana as Medicine 1 (2013) (concluding there is no current scientific evidence that marijuana is beneficial in any way for the treatment of any psychiatric disorder), *available at* file:///C:/Users/Owner/Downloads/position-2013-marijuana-as-medicine%20(1).pdf; American Society of Addiction Medicine, Public Policy Statement on Marijuana, Cannabinoids and Legalization 4 (2015) (concluding that evidence is uncertain to support the safety and efficacy of cannabis and cannabinoid products to treat medical conditions), *available at* http://asam.org/docs/default-source/public-policy-statements/marijuana-cannabinoids-and-legalization-9-21-20156d6e0f9472bc-604ca5b7ff000030b21a.pdf?sfvrsn=0; American Society for Pain Management Nursing, Statement on the Use of Medical Marijuana 1 (2015) (noting a dearth of quality research and lack of expert consensus to support evidence-based recommendations concerning the clinical use of marijuana), *available at* http://aspmn.org/Documents/Advocacy%20Positions%20Statements/Statement%20on%20the%20use%20of%20Medical%20Marijuana%206-17-2015%20final.pdf; Australian Medical Association, Cannabis Use and Health 12 (2014) (concluding that smoking or ingesting a crude plant product is a risky way to deliver cannabinoids for medical purposes), *available at* https://ama.com.au/position-statement/cannabis-use-and-health-2014; Canadian Medical Association, New "Marihuana for Medical Purposes Regulations": What do Doctors Need to Know? 1 (2014) (concluding there is insufficient scientific evidence to support the use of marijuana for clinical purposes), *retrieved from* https://cma.ca/En/Pages/medical-marijuana.aspx; National Association of Alcohol and Drug Abuse Counselors, NAADAC Position Statement on the Medical and Recreational Use of Marijuana 1 (2013) (taking a position against marijuana as medicine), *available at* http://naadac.org/assets/1959/naadac_position_statement_-_recreational_marijuana_aar_spr2013.pdf; National Association of Drug Court Professionals, Position Statement on Marijuana 4 (2012) (opposing medical marijuana in part because most leading scientific organizations do not support its use), *available at* http://ndcrc.org/sites/default/files/nadcp_board_position_statement_-_marijuana.pdf; National Association of School Nurses, Marijuana and Children 1 (2014) (concluding there is insufficient scientific evidence to approve smoked marijuana for medical use), *available at* https://nasn.org/PolicyAdvocacy/PositionPapersandReports/NASNPositionStatementsFullView/tabid/462/ArticleId/632/Marijuana-and-Children-Adopted-January-2014; National Center on Addiction and Substance Abuse, Position Statement on Marijuana – Medicalization 2 (2016) (concluding there is not sufficient high-quality evidence to determine whether medical marijuana is safe and effective), *available at* http://centeronaddiction.org/newsroom/position-statements; National Council on Alcoholism and Drug Dependence, Marijuana 5 (2010) (advocating for marijuana to be subjected to the same scientific standards as other dangerous prescription drugs), *available at* https://google.com/search?q=National+Council+on+Alcoholism+and+Drug+Dependence%2C+Position+Statement+in+Opposition+to+Medical+Marijuana&rlz=1C1FERN_enUS591US604&oq=National+Council+on+Alcoholism+and+Drug+Dependence%2C+Position+Statement+in+Opposition+to+Medical+Marijuana&aqs=chrome.69i57.388j0j4&sourceid=chrome&ie=UTF-8; Tuberous Sclerosis Alliance, TS Alliance Position Statement on Medical Marijuana 1 (2014) (concluding that the epilepsy community does not know whether marijuana or its components are safe and effective for medical treatment), *available at* http://tsalliance.org/pages.aspx?content=734; *but see* American Nurses Association, Position Statement in Support of Patients' Access to Therapeutic Marijuana 1 (2008) (concluding that marijuana is shown to be effective for treating a wide range of symptoms in a variety of conditions), *available at* http://nursingworld.org/MainMenuCategories/Policy-Advocacy/Positions-and-Resolutions/ANAPositionStatements/Position-Statements-Alphabetically/In-Support-of-Patients-Safe-Access-to-Therapeutic-Marijuana.pdf); U.S. Pain Foundation, Position Statement – Medical Marijuana 1 (2015) (concluding that medical marijuana can be an effective medication to treat many causes of chronic pain where many traditional chronic pain medications do not), *available at* http://uspainfoundation.org/wp-content/uploads/2015/12/Medical-Marijuana-Position-Statement-1.pdf.

17 For a discussion of the measured health benefits of marijuana, see *infra* notes 35 to 37 and accompanying text.

18 See *infra* notes 36 to 37 and accompanying text.

19 Pub. L. No. 91–513, Title II, § 101, Oct. 27, 1970, 84 Stat. 1242, codified at 21 U.S.C. § 801 et seq.

20 21 U.S.C. § 812 (b)(1).

21 *Id.* at § 812 (b)(2)-(5).

22 U.S. Food, Drug, and Cosmetic Act, codified at 21 U.S.C. § 355 et seq.; 21 C.F.R. § 312 et seq. For a synopsis of the FDA approval process, *see* U.S. Food and Drug Administration, The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective (last updated 2014), *at* http://fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.

23 *See* U.S. Food and Drug Administration, Applications for FDA Approval to Market a

New Drug, Adequate and Well-Controlled Studies, 21 C.F.R. § 314.126 (revised as of April 1, 2016).

24 *See generally* U.S. Food and Drug Administration, Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format (2011) [hereafter Warnings for Prescription Drugs], *available at* http://fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.

25 *See generally* U.S. Food and Drug Administration, How Does FDA Decide When a Drug is Not Safe Enough to Stay on the Market?, *at* http://fda.gov/aboutfda/transparency/basics/ucm194984.htm (last updated May 12, 2016). For example, the FDA withdrew the weight loss medications Fenfluramine and Dexfenfluramine from the market in response to studies reporting an association between their use and heart valve disease. *See* U.S. Food and Drug Administration, Questions and Answers About Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux), *at* http://fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm (last updated July 7, 2005). At the time, these medications had commonly been prescribed in combination with another medication, Phentermine, and the combined compound was popularly referred to as "Fen-Phen."

26 U.S. Food and Drug Administration, FDA and Marijuana: Questions and Answers (2016), *at* http://fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm#notapproved.

27 *See* U.S. Food and Drug Administration, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (last updated July 22, 2016), *available at* http://accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=018651&TABLE1=OB_Rx; http://accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm.

28 *See generally* Nora D. Volkow, The Biology and Potential Therapeutic Effects of Cannabidiol (2015), *available at* https://drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/biology-potential-therapeutic-effects-cannabidiol.

29 *See generally* Shauncy Ferro, *Why It's So Hard for Scientists to Study Medical Marijuana*, POPULAR SCI. (April 18, 2013), *available at* http://popsci.com/science/article/2013-04/why-its-so-hard-scientists-study-pot.

30 *See generally* National Institute on Drug Abuse, NIDA's Role in Providing Marijuana for Research, *at* https://drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research (revised August 2016).

31 *See* American Academy of Family Physicians, *supra* note 16, at 1 (requesting that the FDA change marijuana's classification to facilitate clinical research); American Academy of Neurology, *supra* note 16, at 1 (requesting reclassification of marijuana from Schedule I to improve access for approved scientific protocols); American Academy of Pediatrics, *supra* note 16, at 2 (recommending changing marijuana to Schedule II to facilitate research); American College of Physicians, *supra* note 16, at 1 (urging an evidence-based review of marijuana's status as a Schedule I controlled substance); American Epilepsy Society, *supra* note 16, at 1 (urging that marijuana's status as a DEA Schedule I controlled substance be reviewed); American Medical Association, *supra* note 16, at 1 (calling on the FDA to create a special schedule for marijuana with the goal of facilitating clinical research); American Nurses Association, *supra* note 16, at 1 (calling for the FDA to reschedule marijuana to reduce restrictions on research); Tuberous Sclerosis Alliance, *supra* note 16, at 1 (supporting a review of marijuana's status as a DEA Schedule I controlled substance).

32 *See generally* Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 FED. REG. 53687 (Aug. 12, 2016) (to be codified at 21 C.F.R. Chap. II Pt. 1301).

33 *Id.* at 53688.

34 *Id.* at 53689.

35 *See* Kevin P. Hill, *Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review*, 313 J. AM. MED. ASS'N. 2474, 2477 (2015) (concluding there is high-quality evidence from multiple randomized clinical trials that marijuana is effective for treating chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis); Barbara S. Koppel et al., *Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders*, 82 NEUROLOGY 1556, 1556 (2014) (concluding marijuana is probably effective for treating spasticity and central pain); Ziva D. Cooper & Margaret Haney, *Sex-Dependent Effects of Cannabis-Induced Analgesia*, 167 DRUG & ALCOHOL DEPENDENCE 112, 117 (2016) (finding the analgesic effects of marijuana are greater for males than for females).

36 *See* Penny F. Whiting et al., *Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis*, 313 J. AM. MED. ASS'N. 2456, 2467 (2015) (finding moderate-quality evidence that pharmaceutical cannabinoids treat chronic pain and spasticity effectively).

37 *See* Christopher Munsey, *Medicine or Menace? Psychologists' Research Can Inform Debate Over Legalizing Marijuana*, 41 MONITOR ON PSYCHOL. 50, 53 (2010) (concluding that dronabinol at adequate doses achieves the same effects as marijuana on appetite and weight gain); National Institute on Drug Abuse, DrugFacts: Is Marijuana Medicine? 3 (2015) (concluding that dronabinol and nabilone are effective for treating nausea caused by chemotherapy and appetite loss in patients with wasting illness caused by AIDS), *available at* https://drugabuse.gov/publications/drugfacts/marijuana-medicine; *but see* Penny F. Whiting et al., *supra*, at 2467 (concluding evidence is low quality for effects of pharmaceutical cannabinoids on nausea, vomiting and weight gain).

38 *See, e.g.*, Kevin P. Hill, *supra* note 35, at 2477 (recommending that treatment be initiated with dronabinol or nabilone and escalated to include marijuana only if these are not successful).

39 *See* Barbara S. Koppel et al., *supra* note 35, at 1556 (concluding that marijuana is probably ineffective for treating bladder complaints and its effects are unknown for epilepsy and movement disorders); D. Gloss & B. Vickrey, *Cannabinoids for Epilepsy*, 3 COCHRANE DATABASE SYSTEMATIC REV. (2014) (concluding no reliable conclusions can be drawn concerning the efficacy of cannabinoids for treating epilepsy), *available at* http://ncbi.nlm.nih.gov/pubmed/24595491; American Epilepsy Society, *supra* note 16, at 1 (concluding robust scientific evidence is lacking to support marijuana for treating epilepsy); Kevin P. Hill, *supra* note 35, at 2477 (concluding only preliminary studies suggest marijuana might be effective for glaucoma).

40 *See* Kevin P. Hill, *supra* note 35, at 2477 (concluding that the evidence supporting marijuana and cannabinoids for conditions other than chronic pain, neuropathic pain, and spasticity is "either equivocal or weak"); Michael Shermer, *The Quack of the Gaps Problem: Facilitated Communication, Autism and Patients' Rights*, Scientific American 75 (August, 2016) (noting the long list of failed treatments for autism includes marijuana); Deidre A. Conroy et al., *Marijuana Use Patterns and Sleep Among Community-Based Young Adults*, 35 J. ADDICTIVE DISEASES 135 (2016) (finding that symptoms of insomnia and sleep disturbances were worse for participants using marijuana on a daily basis), *available at* doi:10.1080/10550887.2015.1132986.

41 *See* Kevin P. Hill, *supra* note 35, at 2478 (concluding that marijuana is contraindicated for patients with substance use, anxiety, mood, and psychotic disorders); Efrat Aharonovich et al., *Postdischarge Cannabis Use and its Relationship to Cocaine, Alcohol, and Heroin Use: A Prospective Study*, 162 AM. J. PSYCHIATRY 1507, 1511 (2005) (finding higher relapse rates for patients in substance use disorder treatment when they used marijuana); Mohammadali Mojarrad et al., *Marijuana Use and Achievement of Abstinence from Alcohol and Other Drugs Among People with Substance Dependence: A Prospective Cohort Study*, 142 DRUG & ALCOHOL DEPENDENCE 91, 94 (2014) (same); M. Alvarez-Jimenez et al., *Risk Factors for Relapse Following Treatment for First Episode Psychosis: A Systematic Review and Meta-Analysis of Longitudinal Studies*, 139 SCHIZOPHRENIA RES. 116 (2012) (finding higher relapse rates for patients with psychotic disorders when they used marijuana); Rashmi Patel et al., *Association of Cannabis Use with Hospital Admission and Antipsychotic Treatment Failure in First Episode Psychosis: An Observational Study*, 6 BRIT. MED. J. e009888 (same), *available at* doi:10.1136/bmjopen-2015-009888; Marcel O. Bonn-Miller et al., *Prospective Investigation of the Impact of Cannabis Use Disorders on Posttraumatic Stress Disorder Symptoms Among Veterans in Residential Treatment*, 5 PSYCHOLOGICAL TRAUMA: THEORY, RES. & PRACT. 193, 196 (2013) (finding poorer outcomes in PTSD treatment for military veterans with cannabis use disorders).

42 *See* Timothy Caulfield & Colin Feasby, *supra* note 14, at 186-7 (reviewing studies finding that approximately 20% to 50% of citizens in the United States, Canada, France, Denmark and Australia make use of alternative medical treatments); Aimee Doyle, *Alternative Medicine and Medical Malpractice*, 22 J. LEGAL MED. 533, 534 (2001) (noting that nearly 60% of mainstream physicians refer patients for alternative therapies) (citing J. Borkan et

continued on page 14

continued from page 13

al., *Referrals for Alternative Therapies*, 39 J. FAM. PRAC. 545 (1994)); Stephen Bent, *Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation*, 23 J. GEN. INTERNAL MED. 854, 854 (2008) (noting that 20% of the U.S. population has used herbal products); Edzard Ernst, *Prescribing Herbal Medications Appropriately*, 53 J. FAM. PRAC. 985, 985 (2004) (noting the percentage of patients using herbal medications increased nearly 400% from 1990 to 1997).

43 Pub. L. No. 103-417, Oct. 25, 1994, 108 Stat. 4325, codified at 21 U.S.C. § 301 *et seq.*

44 21 U.S.C. § 342. Importantly, draft guidance from the FDA suggests that botanical products which are intended to treat disease may be regulated as a drug rather than a dietary supplement. *See* U.S. Food and Drug Administration, Guidance for Industry on Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration: Draft Guidance for Comment 3-4 (2006), *available at* http://fda.gov/OHRMS/DOCKETS/98FR/06D-0480-GLD0001.PDF (last updated December 1, 2006). If this provision is ultimately adopted, medical marijuana products could potentially be subjected to the FDA approval process.

45 See *supra* notes 22 to 25 and accompanying text.

46 *See generally* David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES GEN. PSYCHIATRY 1021 (2006) (finding that 21% of prescriptions were for off-label use).

47 *See* Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (noting that off-label use of medications is legal and common).

48 *Id.* (noting that off-label use of medications is often unsupported by strong evidence).

49 *See generally* Dieter Giesen, *Civil Liability of Physicians for New Methods of Treatment and Experimentation: A Comparative Examination*, 3 MED. L. REV. 22 (1995) (differentiating innovative therapy from traditional and experimental therapies); MICHAEL H. COHEN, COMPLEMENTARY AND ALTERNATIVE MEDICINE: LEGAL BOUNDARIES AND REGULATORY PERSPECTIVES (1998) (defining alternative and complementary therapies); J. Brad Kallmayer, *A Chimera in Every Sense: Standard of Care for Physicians Practicing Complementary and Alternative Medicine*, 2 IND. HEALTH L. REV. 225 (2005).

50 *See generally Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (finding no constitutional right for terminally ill patients to receive experimental drugs undergoing lengthy FDA approval).

51 *See Schneider v. Revici*, 817 F.2d 987, 995 (2d. Cir. 1987) (finding no reason patients should not be allowed to forego currently approved medical treatments in search of unconventional remedies).

52 *See* Aimee Doyle, *supra* note 42, at 548 (recommending that physicians providing alternative treatments obtain comprehensive informed consent akin to what is required for experimental treatments) (citing Kathleen M. Boozang, *Western Medicine Opens the Door to Alternative Medicine*, 24 AM. J. L. & MED. 185, 187 (1998)); Timothy Caulfield & Colin Feasby, *supra* note 14, at 195 (same); *Schneider v. Revici*, *supra*, at 996 (finding that a patient may make an informed decision to seek unconventional treatment pursuant to a carefully documented consent form). For further discussion of recommended informed consent procedures for medical marijuana, see *infra* notes 117 to 132 and accompanying text.

53 *See* WORLD HEALTH ORG., THE HEALTH AND SOCIAL EFFECTS OF NONMEDICAL CANNABIS USE 40 (2016) (concluding that the risk of dependence for marijuana is approximately 1 in 10 among those who ever used the drug, 1 in 6 among adolescent users, and 1 in 3 among daily users), *available at* http://who.int/substance_abuse/publications/cannabis_report/en/; Nora D. Volkow et al., *Adverse Health Effects of Marijuana Use*, 370 NEW ENG. J. MED. 2219, 2219-20 (2014) (concluding that marijuana is addictive for approximately 9% of those who experiment with the drug, approximately 1 out of 6 people who start using it as a teenager, and 25% to 50% of daily users); Kevin P. Hill, *supra* note 35, at 2478 (concluding marijuana is addictive for 9% of adult users and 17% of adolescent users); Peggy van der Pol et al., *Predicting the Transition From Frequent Cannabis Use to Cannabis Dependence: A Three-Year Prospective Study*, 133 DRUG & ALCOHOL DEPENDENCE 352, 354 (2013) (finding 37% dependence liability for frequent marijuana users); James C. Anthony et al., *Comparative Epidemiology of Dependence on Tobacco, Alcohol, Controlled Substances, and Inhalants: Basic Findings From the National Comorbidity Study*, 2 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 244, 251. tbl.2 (1994) (finding 9% dependence liability for marijuana users in a national U.S. study); F. A. Wagner & James C. Anthony, *From First Drug Use to Drug Dependence: Developmental Periods of Risk for Dependence Upon Marijuana, Cocaine, and Alcohol*, 26 NEUROPSYCHOPHARMACOLOGY 479 (2002) (finding 8% dependence liability for marijuana users in a national study); Alan J. Budney & B. A. Moore, *Development and Consequences of Cannabis Dependence*, 42 J. CLINICAL PHARMACOLOGY 1S, 29S (2002) (concluding the dependence liability for marijuana is 9% overall, 20% to 30% for those have used marijuana at least 5 times, and 35% to 40% for those who use marijuana daily).

54 *See* Nora D. Volkow et al., *supra* note 53, at 2219 (noting there is a consensus among scientists that marijuana produces a bona fide withdrawal syndrome characterized by irritability, sleeping difficulties, depression, drug cravings, and anxiety); Alan J. Budney et al., *Marijuana Abstinence Effects in Marijuana Smokers Maintained in their Home Environment*, 58 ARCHIVES GEN. PSYCHIATRY 917 (2001); U. W. Preuss et al., *Cannabis Withdrawal Severity and Short-term Course Among Cannabis-Dependent Adolescent and Young Adult Inpatients*, 106 DRUG & ALCOHOL DEPENDENCE 133 (2010); Philip H. Smith et al., *Marijuana Withdrawal and Aggression Among a Representative Sample of U.S. Marijuana Users*, 132 DRUG & ALCOHOL DEPENDENCE 63 (2013).

55 *See* AM. PSYCHIATRIC ASS'N., DIAGNOSTIC & STATISTICAL MANUAL OF MENTAL DISORDERS 175-6 (3d ed. 1980); AM. PSYCHIATRIC ASS'N., DIAGNOSTIC & STATISTICAL MANUAL OF MENTAL DISORDERS 176-7 (3d ed. rev. 1987); AM. PSYCHIATRIC ASS'N., DIAGNOSTIC & STATISTICAL MANUAL OF MENTAL DISORDERS 216 (4th ed. 1994); AM. PSYCHIATRIC ASS'N., DIAGNOSTIC & STATISTICAL MANUAL OF MENTAL DISORDERS 236 (4TH ed. text rev. 2000).

56 *See* AM. PSYCHIATRIC ASS'N., DIAGNOSTIC & STATISTICAL MANUAL OF MENTAL DISORDERS 517-9 (5th ed. 2013); *see also* Jordon P. Davis et al., *Cannabis Withdrawal, Posttreatment Abstinence, and Days to First Cannabis Use Among Emerging Adults in Substance Use Treatment: A Prospective Study*, 46 J. DRUG ISSUES 64, 76 (2016) (finding that cannabis withdrawal increases the risk of treatment failure and relapse to cannabis use).

57 *See* Nora D. Volkow et al., *Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review*, 73 J. AM. MED. ASS'N. 292, 293 (2016) (concluding from preclinical and clinical studies that cannabis use is associated with an amotivational state).

58 *Id.* at 294.

59 *See* U.S. Food and Drug Administration, Warnings for Prescription Drugs, *supra* note 24, at 3 (requiring a package insert or box warning if an adverse reaction associated with a drug could result in a "substantial disruption of the ability to conduct normal life functions").

60 *See generally* Nora D. Volkow et al., *supra* note 57, at 292; E. A. Osuch et al., *Depression, Marijuana Use and Early-Onset Marijuana Use Conferred Unique Effects on Neural Connectivity and Cognition*, 134 ACTA PSYCHIATRICA SCANDINAVICA 399 (2016) (finding that frequent marijuana use was associated with changes in neuronal connectivity in brain regions responsible for motor planning, motor control, ventral emotion, and reward processing).

61 *See generally* Jon E. Grant et al., *Neuropsychological Deficits Associated with Cannabis Use in Young Adults*, 121 DRUG & ALCOHOL DEPENDENCE 159 (2012); Michael T. Kucewicz et al., *Dysfunctional Prefrontal Cortical Network Activity and Interactions Following Cannabinoid Receptor Activation*, 31 J. NEUROSCIENCE 15560 (2011).

62 *See generally* A.M. Schreiner et al., *Residual Effects of Cannabis Use on Neurocognitive Performance After Prolonged Abstinence: A Meta-Analysis*, 20 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 420 (2012).

63 *See generally* Madeline H. Meier et al., *Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife*, PROC. NAT'L ACAD. SCI. (2012), *available at* www.pnas.org/cgi/

doi/10.1073/pnas.1206820109; E. A. Osuch et al., *supra* note 60, at 402 (finding that early onset marijuana use was associated with significantly lower total and verbal IQ scores).

64 *See* Madeline H. Meier et al., *supra*, at E2659, E2661; Michael Takagi et al., *Verbal Memory, Learning, and Executive Functioning Among Adolescent Inhalant and Cannabis Users*, 72 J. STUD. ALCOHOL & DRUGS 96, 102 (2011); K. I. Bolla et al., *Dose-related Neurocognitive Effects of Marijuana Use*, 50 NEUROLOGY 1337 (2002).

65 *See* Madeline H. Meier et al., *supra*, at E2661.

66 *See generally* Amelia M. Arria at el., *Marijuana Use Trajectories During College Predict Health Outcomes Nine Years Post-Matriculation*, 159 DRUG & ALCOHOL DEPENDENCE 158 (2016).

67 *See generally* Motoaki Hara et al., *Concurrent Life-Course Trajectories of Employment and Marijuana-use: Exploring Interdependence of Longitudinal Outcomes*, 45 J. SUBSTANCE ABUSE TREATMENT 426 (2013), *available at* http://journalofsubstanceabusetreatment.com/article/S0740-5472(13)00115-3/abstract.

68 *See generally* Jane A. Fischer et al., *Cannabis Use and Quality of Life of Adolescents and Young Adults: Findings from an Australian Birth Cohort*, 47 J. PSYCHOACTIVE DRUGS 107 (2015).

69 *See generally* Anna-Karin Danielsson et al., *Cannabis Use in Adolescence and Risk of Future Disability Pension: A 39-Year Longitudinal Cohort Study*, 143 DRUG & ALCOHOL DEPENDENCE 239 (2014).

70 *See generally* Christian Thurstone et al., *Medical Marijuana Diversion and Associated Problems in Adolescent Substance Treatment*, 118 DRUG & ALCOHOL DEPENDENCE 489 (2011) (finding that 49% of adolescents in substance use disorder treatment reported obtaining marijuana from someone with a medical marijuana card), *available at* http://ncbi.nlm.nih.gov/pubmed/21565453; Joseph J. Palamar et al., *Correlates of Intentions to Use Cannabis Among US High School Seniors in the Case of Cannabis Legalization*, 118 INT'L J. DRUG POL'Y 489 (2014) (finding in a national U.S. survey that 10% of non-marijuana-using adolescents intended to use marijuana if it were legalized), *available from* http://dx.doi.org/10.1016/j.drugpo.2014.01.017; Jane C. Maxwell & Bruce Mendelson, *supra* note 2, at 10 (finding that adolescent perceptions about the dangers of marijuana decreased significantly in states that legalized marijuana for medicinal or recreational use); *see also* Magdalena Cerda et al., *Medical Marijuana Laws in 50 States: Investigating the Relationship Between State Legalization of Medical Marijuana and Marijuana Use, Abuse and Dependence*, 120 DRUG & ALCOHOL DEPENDENCE 22 (2010) (finding significantly higher rates of marijuana use, abuse and dependence in states with medical marijuana laws), *available at* http://drugandalcoholdependence.com/article/S0376-8716(11)00274-2/abstract; Joseph Schuermeyer et al., *Temporal Trends in Marijuana Attitudes, Availability and Use in Colorado Compared to Non-Medical Marijuana States: 2003-11*, 140 DRUG & ALCOHOL DEPENDENCE 145 (2014) (finding that legalization of marijuana in Colorado was associated with a lower perception of risks from marijuana and potentially higher rates of marijuana abuse and dependence), *available at* http://ncbi.nlm.nih.gov/pubmed/24837585.

71 *See* Namkee G. Choi et al., *Older-Adult Marijuana Users and Ex-Users: Comparisons of Sociodemographic Characteristics and Mental and Substance Use Disorders*, 165 DRUG & ALCOHOL DEPENDENCE 94, 100-101 (2016) (finding that older adult marijuana users had high rates of mental health disorders warranting clinical attention).

72 *See generally* Jodi M. Gilman et al., *Cannabis Use is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users*, 34 J. NEUROSCIENCE 5529 (2014).

73 *See generally* Young-Hoon Sung et al., *Decreased Frontal N-Acetylaspartate Levels in Adolescents Concurrently Using Both Methamphetamine and Marijuana*, 246 BEHAV. BRAIN RES. 154 (2013), *available at* http://dx.doi.org/10.1016/j.bbr.2013.02.028; Michael T. Kucewicz et al., *supra* note 61.

74 *See generally* Michael A. P. Bloomfield et al., *The Link Between Dopamine Function and Apathy in Cannabis Users: An [18F]-DOPA PET Imaging Study*, 231 PSYCHOPHARMACOLOGY 2251 (2014), *available at* doi:10.1007/s00213-014-3523-4.

75 *See generally* Mark Asbridge et al., *Acute Cannabis Consumption and Motor Vehicle Collision Risk: Systematic Review of Observational Studies and Meta-analysis*, 344 BRIT. MED. J. e536 (2012), *available at* doi:10.1136/bmj.e536; Mu-Chen Li et al., *Marijuana Use and Motor Vehicle Crashes*, 34 EPIDEMIOLOGICAL REV. 65 (2011), *available at* doi:10.1093/epirev/mxr017; Rebecca L. Hartman & Marilyn A. Huestis, *Cannabis Effects on Driving Skills*, 59 CLINICAL CHEMISTRY (2012), *available at* http://hwmaint.clinchem.org/cgi/doi/10.1373/clinchem.2012.194381.

76 *See* Rebecca L. Hartman & Marilyn A. Huestis, *supra*, at 1.

77 *See* UNITED NATIONS OFF. DRUGS & CRIME, CANNABIS: A SHORT REVIEW 4 (n.d.) (concluding that marijuana negatively affects reaction time, attention, motor performance, coordination, and information processing for up to 28 days after abstinence), *available at* https://unodc.org/documents/drug-prevention-and-treatment/cannabis_review.pdf; Wendy M. Bosker et al., *Psychomotor Function in Chronic Daily Cannabis Smokers During Sustained Abstinence*, 8 PLoS ONE e53127 (2013) (finding that impairments in critical tracking and divided attention skills were observable after 3 weeks of abstinence), *available at* doi:10.1371/journal.pone.0053127.

78 *See* ROCKY MOUNTAIN HIGH INTENSITY DRUG TRAFFICKING AREA, THE LEGALIZATION OF MARIJUANA IN COLORADO: THE IMPACT 2 (2015), *available at* http://rmhidta.org/html/2015%20final%20legalization%20of%20marijuana%20in%20colorado%20the%20impact.pdf; Stacy Salomonsen-Sautel et al., *Trends in Fatal Motor Vehicle Crashes Before and After Marijuana Commercialization in Colorado*, 140 DRUG & ALCOHOL DEPENDENCE 137 (2013), *available at* http://dx.doi.org/10.1016/j.drugalcdep.2014.04.008.

79 *See generally* Rajiv Radhakrishnan et al., *Gone to Pot – A Review of the Association Between Cannabis and Psychosis*, 5 FRONT PSYCHIATRY ONLINE (2016) (concluding that marijuana can be a component cause of psychotic disorders but is neither necessary nor sufficient for the condition), *at* http://ncbi.nlm.nih.gov/pubmed/24904437; David J. Castle, *Cannabis and Psychosis: What Causes What?*, 5 MED. REP. ONLINE (2013) (same), *at* http://ncbi.nlm.nih.gov/pubmed/23361396; Matthew Large et al., *Cannabis Use and Earlier Onset of Psychosis, A Systematic Meta-analysis*, 68 ARCHIVES GEN. PSYCHIATRY 555 (2011) (finding the average age of onset of psychosis is 2.7 years sooner for marijuana users than nonusers), *available at* doi:10.1001/archgenpsychiatry.2011.5; Nora D. Volkow et al., *supra* note 57, at 294 (concluding from longitudinal studies that marijuana use precedes psychosis after controlling statistically for alcohol and other drug consumption).

80 *See generally* Marta Di Forti et al., *Confirmation that the AKT1 (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users*, 72 BIOLOGICAL PSYCHIATRY 811 (2012); *see also* Rajiv Radhakrishnan et al., *supra*, at 23 (concluding that genetic factors confer a vulnerability to psychosis from marijuana exposure).

81 *See generally* Tabea Schoeler et al., *Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis*, 73 J. AM. MED. ASS'N. PSYCHIATRY 191 (2016) (finding a dose-dependent relationship between continued marijuana use and psychiatric rehospitalizations for patients following an initial psychotic episode); Nora D. Volkow, *supra* note 57, at 294; M. Alvarez-Jimenez et al., *supra* note 41; Rashmi Patel et al., *supra* note 41.

82 *See generally* EDWARD V. NUNES ET AL., SUBSTANCE DEPENDENCE AND CO-OCCURRING PSYCHIATRIC DISORDERS: BEST PRACTICES FOR DIAGNOSIS AND CLINICAL TREATMENT (Civic Research Inst., 2010); Stephen Ross, *The Mentally Ill Substance Abuser, in* TEXTBOOK OF SUBSTANCE ABUSE TREATMENT 537 (4th ed., Marc Galanter & Herbert D, Kleber eds., 2008); Daniel Rasic et al., *Longitudinal Associations of Cannabis and Illicit Drug Use With Depression, Suicidal Ideation and Suicidal Attempts Among Nova Scotia High School Students*, 129 DRUG & ALCOHOL DEPENDENCE 49 (2013).

83 *See generally* Melanie Gibbs et al., *Cannabis Use and Mania Symptoms: A Systematic Review and Meta-Analysis*, 171 J. AFFECTIVE DISORDERS 39 (2015); David W. Brook et al., *Drug Use and the Risk of Major Depressive Disorder, Alcohol Dependence, and Substance Use Disorders*, 50 ARCH. GEN. PSYCHIATRY 1039 (2002); Matthew Large et al., *supra* note 79; Russell C. Callaghan et al., *Methamphetamine Use and Schizophrenia: A Population-Based Cohort Study in California*, 169 AM. J. PSYCHIATRY 389 (2012); *but see* Marcel O. Bonn-Miller et al., *Cannabis Use Among Military Veterans After Residential Treatment for Posttraumatic Stress Disorder*, 25 PSYCHOLOGY ADDICTIVE BEHAV. 485, 489 (2011) (finding that PTSD symptoms typically occurred prior to marijuana use among military veterans).

84 *See generally* Carlos Blanco et al., *Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence from a US National Longitudinal Study*, 72 J. AM. MED. ASS'N. 388 (2016), *available at* doi:10.1001/jamapsychiatry.2015.3229.

continued on page 16

continued from page 15

85 *See* Carlos Blanco et al., *supra* note 84, at E5; David W. Brook et al., *supra* note 83.

86 *See generally* Anna-Karin Danielsson et al., *Cannabis Use and Psychological Distress: An 8-Year Prospective Population-Based Study Among Swedish Men and Women*, 59 ADDICTIVE BEHAV. 18 (2016) (finding significantly higher rates of psychological distress after 8 years among female marijuana users than nonusers, but no differences for males).

87 *See generally* Nadav Shalit et al., *The Association Between Cannabis Use and Suicidality Among Men and Women: A Population-Based Longitudinal Study*, 205 J. AFFECTIVE DISORDERS 216 (2016) (finding significantly higher rates of suicidality among male marijuana users after 3 years compared to nonusers, but no differences for females), *available at* http://dx.doi.org/10.1016/j.jad.2016.07.010.

88 *See generally* Efrat Aharonovich et al., *supra* note 41, at 1511; Mohammadali Mojarrad et al., *supra* note 41, at 94.

89 *See generally* Jeanette M. Tetrault et al., *Effects of Marijuana Smoking on Pulmonary Function and Respiratory Complications: A Systematic Review*, 167 ARCHIVES INTERNAL MED. 221 (2007) (concluding that long-term marijuana smoking is associated with increased respiratory symptoms suggestive of obstructive lung disease); National Institute on Drug Abuse, DrugFacts: Marijuana 3, at https://drugabuse.gov/publications/drugfacts/marijuana (revised March 2016).

90 *See* National Institute on Drug Abuse, *supra*, at 3; *see also* Barbara S. Koppel et al., *supra* note 39, at 1561 (finding 1% risk of serious adverse health events from medical marijuana).

91 *See* BRIT. LUNG FOUND., THE IMPACT OF CANNABIS ON YOUR LUNGS 6 (2012), *available at* http://drugsandalcohol.ie/17670/1/The_impact_of_cannabis_on_your_lungs_-_BLF_report_2012.pdf.

92 *See* National Institute on Drug Abuse, *supra* note 89, at 3.

93 *See* American College of Obstetricians and Gynecologists, *supra* note 16, at 2-3 (concluding that marijuana may impair the neurodevelopment of a fetus).

94 *See generally* Tina D. Gundersen et al., *Association Between Use of Marijuana and Male Reproductive Hormones and Semen Quality: A Study of 1,215 Healthy Young Men*, AM. J. EPIDEMIOLOGY (2016), *at* doi:10.1093/aje/kwv135.

95 *See* MARK A. HALL ET AL., MEDICAL LIABILITY AND TREATMENT RELATIONSHIPS 169-170 (3rd ed., Wolters Kluwer, 2013) (noting that courts find enhanced protections for medical patients based on the implied or expressed belief that the treatment relationship is a fiduciary one in which physicians owe heightened duties to protect the vulnerable patient's interests).

96 *Id.* at 114-115.

97 *Id.* (citing, in part, *Crisp Regional Hospital v. Oliver*, 621 S.E.2d 554, 560-561 (Ga. App. 2005); *White v. Harris*, 36 A.2d 203 (Vt. 2011)).

98 *See, e.g.*, *McCourt v. Abernathy*, 457 S.E.2d 603, 606-607 (S.C. 1995) (upholding jury instruction applying custom-based standard of care in a medical malpractice case).

99 *See, e.g., Locke v. Pachtman*, 446 Mich. 216, 222 (1994) (noting the long-recognized importance of expert testimony in establishing the custom-based standard of care in medical malpractice cases).

100 *See* Philip G. Peters, *The Role of the Jury in Modern Malpractice Law*, 87 IOWA L. REV. 909, 913 (2002) (noting that a custom-based standard defers conclusively to medical opinion and removes other evidence concerning reasonable medical practice from jury consideration), *available at* http://scholarship.law.missouri.edu/cgi/viewcontent.cgi?article=1311&context=facpubs.

101 *Id.* at 913-916 (reviewing movement away from custom-based standard to a reasonable physician standard).

102 *See* Timothy Caulfield & Colin Feasby, *supra* note 14, at 198-200 (discussing the emergence of evidence-based medicine and its implications in malpractice actions for reasonable medical practices).

103 See *supra* note 16 and accompanying text.

104 *See, e.g., Stang-Starr v. Byington*, 532 N.W.2d 26, 30 (Neb. 1995) (finding that learned treatises and similar publications may be admissible to impeach, contradict or discredit a witness but not as evidence to support an opinion or theory).

105 *See* MARK A. HALL ET AL., *supra* note 95, at 377-378 (citing in part Federal Rules of Evidence 701, 702, 703 & 803).

106 *See* U.S. Pain Foundation, *supra* note 16, at 1 (concluding that people living with chronic illness and pain should have access to timely and appropriate treatments, which includes medical marijuana); American Nurses Association, *supra* note 16, at 1 (concluding that marijuana has been shown to be effective in treating a wide range of symptoms in a variety of conditions).

107 See *supra* notes 35 to 37 and accompanying text.

108 *See, e.g., Jones v. Chidester*, 531 Pa. 31, 40, 610 A.2d 964 (1992) (finding that two schools of thought is an absolute defense to medical malpractice).

109 *See, e.g.*, Brennen McKenzie, Complementary and Alternative Medicine (CAM) and the Law Part 3: Malpractice 3, *at* https://sciencebasedmedicine.org/cam-and-the-law-part-3-malpractice/ (last updated October, 2016).

110 *See, e.g., Jones v. Chidester, supra*, 531 Pa. 31, 40.

111 *See, e.g., Chumbler v. McClure*, 505 F.2d 489, 492 (6th Cir. 1974) (finding that a reasonable division of medical opinion is sufficient to direct a verdict for the defendant).

112 *See, e.g.*, California Dept. of Public Health, *supra* note 9; Massachusetts Department of Public Health, *supra* note 9.

113 *See* American Society of Addiction Medicine, The Role of the Physician in "Medical" Marijuana 38-39 (2010), *available at* http://asam.org/docs/publicy-policy-statements/1role_of_phys_in_med_mj_9-10.pdf?sfvrsn=0; Kevin P. Hill, *supra* note 35, at 2478-2480.

114 *See* Timothy Caulfield & Colin Feasby, *supra* note 14, at 200 (concluding that professional practice guidelines are likely to be viewed as powerful, although not conclusive, evidence of the legal standard of care).

115 *See* MARK A. HALL ET AL., *supra* note 95, at 434-435 (reviewing assumption of the risk doctrine in medical malpractice cases).

116 *Id.* at 435 (noting that a patient's waiver of liability for a physician's negligent performance of substandard care is unenforceable as contrary to public policy).

117 *See generally Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir.), *cert. den'd*, 409 U.S. 1064 (1972).

118 *See generally id.*

119 *See* MARK A. HALL ET AL., *supra* note 95, at 214 (noting that about half of states follow a professional custom test for disclosure in informed consent cases); *Culbertson v. Mernitz*, 602 N.E.2d 98 (Ind. 1992) (adopting a professional custom standard for disclosure).

120 *See* John A. Astin, *Why Patients Use Alternative Medicine: Results of a National Study*, 279 J. AM. MED. ASS'N. 1548, 1552 (1998) (concluding from a national survey of over 1,000 respondents that "the most influential or salient factor in people's decision [sic] to use alternative health care may be its perceived efficacy"); Joshua M. Baumi et al., *Do Attitudes and Beliefs Regarding Complementary and Alternative Medicine Impact its Use Among Patients with Cancer? A Cross-Sectional Survey*, 121 CANCER 2431, 2436 tbl.3 (2015) (finding in a study of nearly 1,000 patients that expected health benefits significantly predicted the likelihood of using complementary treatments for cancer).

121 *See* Timothy Caulfield & Colin Feasby, *supra* note 14, at 193-4 (reviewing dangerous side effects of herbal remedies that many consumers are unaware of); Kah Hoong Chang et al., *Complementary and Alternative Medicine Use in Oncology: A Questionnaire Survey of Patients and Health Care Professionals*, 11 BIOMED CENTRAL CANCER 196, 196-7 (2011), *available at* http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-11-196.

122 *See, e.g.*, Timothy Caulfield & Colin Feasby, *supra* note 14, at 195 (concluding that the proven safety, efficacy or lack of efficacy of a treatment clearly has the potential to influence treatment decisions, and as such is something a reasonable person in the patient's position would want to know).

123 *See, e.g., Rizzo v. Schiller*, 445 S.E.2d 153 (Va. 1994) (finding that a general consent form is insufficient to satisfy the duty of disclosure); *Schneider v. Revici*, *supra* note 51, at 996 (finding that a patient may make an informed decision to seek unconventional treatment pursuant to a carefully documented consent form).

124 *See* MARK A. HALL ET AL., *supra*, note 95, at 217 (noting that most jurisdictions apply an objective causation standard in informed consent cases).

Neuroscience and Biobehavioral Reviews 126 (2021) 175–193

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Determining the magnitude and duration of acute Δ^9-tetrahydrocannabinol (Δ^9-THC)-induced driving and cognitive impairment: A systematic and meta-analytic review

Danielle McCartney [a,b,c,*], Thomas R. Arkell [a,b,c], Christopher Irwin [d,e], Iain S. McGregor [a,b,c]

[a] The University of Sydney, Lambert Initiative for Cannabinoid Therapeutics, Sydney, New South Wales, Australia
[b] The University of Sydney, Brain and Mind Centre, Sydney, New South Wales, Australia
[c] The University of Sydney, Faculty of Science, School of Psychology, Sydney, New South Wales, Australia
[d] School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia
[e] Menzies Health Institute Queensland, Gold Coast, Queensland, Australia

ARTICLE INFO

Keywords:
Cannabis
Marijuana
Δ^9-tetrahydrocannabinol
Driving
Cognitive function
Psychomotor function
Road safety

ABSTRACT

The increasing legal availability of cannabis has important implications for road safety. This systematic review characterised the acute effects of Δ^9-THC on driving performance and driving-related cognitive skills, with a particular focus on the duration of Δ^9-THC-induced impairment. Eighty publications and 1534 outcomes were reviewed. Several measures of driving performance and driving-related cognitive skills (e.g. lateral control, tracking, divided attention) demonstrated impairment in meta-analyses of "peak" Δ^9-THC effects (p's<0.05). Multiple meta-regression analyses further found that regular cannabis users experianced less impairment than 'other' (mostly occasional) cannabis users ($p = 0.003$) and that the magnitude of oral ($n = 243$ effect estimates [EE]) and inhaled ($n = 481$ EEs) Δ^9-THC-induced impairment depended on various factors (dose, post-treatment time interval, the performance domain (skill) assessed) in other cannabis users (p's<0.05). The latter model predicted that most driving-related cognitive skills would 'recover' (Hedges' g=–0.25) within ~5-hs (and almost all within ~7-hs) of inhaling 20 mg of Δ^9-THC; oral Δ^9-THC-induced impairment may take longer to subside. These results suggest individuals should wait at least 5 -hs following inhaled cannabis use before performing safety-sensitive tasks.

1. Introduction

The introduction of legal access to both medical and non-medical cannabis products is a recent global phenomenon that is reframing social, political, and clinical perspectives toward this ancient natural product. A major public health issue concerns the detrimental effects of cannabis use on car driving performance (and other 'safety-sensitive' tasks) and how to provide clear, evidence-based advice and associated legal frameworks to manage cannabis-induced impairment (Macdonald, 2019; Ramaekers, 2018). This requires a comprehensive understanding of cannabis and Δ^9-tetrahydrocannabinol's (Δ^9-THC: the main intoxicating component of cannabis) acute effects on skilled performance.

The deleterious effects of cannabis use on driving have been explored in epidemiological and experimental studies as summarised in recent systematic reviews (Hartman and Huestis, 2013; Li et al., 2012; National Academies of Sciences Engineering and Medicine, 2017; Rogeberg, 2019; Rogeberg and Elvik, 2016, 2017). Findings from epidemiological studies suggest that cannabis use bestows a moderately increased risk of being involved in, or responsible for, a car crash (Rogeberg, 2019; Rogeberg and Elvik, 2016, 2017). Experimental studies in which a fixed dose of Δ^9-THC is administered (e.g. smoked, vaporised, oral) prior to performing a driving test (e.g. simulated, on-road) or a discrete neuropsychological test measuring some driving-related cognitive skill (e.g. information processing, divided attention, tracking performance) have likewise observed an impairing effect (Broyd et al., 2016; Hartman and Huestis, 2013; Oomen et al., 2018), although a comprehensive, meta-analytic review of this evidence is currently lacking. Notably, such effects appear to be less pronounced in regular (compared to occasional) cannabis users, likely due to the development of tolerance (Colizzi and Bhattacharyya, 2018). Some aspects of driving performance also appear

* Corresponding author at: Lambert Initiative for Cannabinoid Therapeutics Brain and Mind Centre, University of Sydney, Camperdown, New South Wales, 2050, Australia.
E-mail address: danielle.mccartney@sydney.edu.au (D. McCartney).

https://doi.org/10.1016/j.neubiorev.2021.01.003
Received 27 August 2020; Received in revised form 24 November 2020; Accepted 4 January 2021
Available online 23 January 2021

to be more susceptible to Δ^9-THC-induced impairment than others. For example, while a number of studies have shown that Δ^9-THC increases standard deviation of lane position (SDLP) ("weaving" during simulated and on-road driving tests) (Arkell et al., 2019; Bosker et al., 2012; Brown et al., 2019; Hartman et al., 2015; Micallef et al., 2018; Ramaekers et al., 2000; Ronen et al., 2008; Veldstra et al., 2015), average driving speed is not typically affected (Anderson et al., 2010a; Arkell et al., 2019; Bosker et al., 2012; Brands et al., 2019; Ronen et al., 2010, 2008).

One of the most critical, yet unresolved, issues relating to cannabis use and road safety is the duration of Δ^9-THC-induced driving impairment. The complex pharmacokinetics of Δ^9-THC (e.g., rapid and transient peak in blood concentrations, lengthy persistence in biological matrices) mean that, unlike alcohol, there is no clear relationship between blood Δ^9-THC concentrations and impairment (Arkell et al., 2020b; Ginsburg, 2019; Madras, 2017). Put simply, it is difficult to determine the point at which Δ^9-THC-induced driving impairment typically subsides. Legal frameworks to manage cannabis-induced impairment are therefore inconsistent (e.g., in some jurisdictions it is illegal to drive with any detectable amount of Δ^9-THC or Δ^9-THC metabolites in blood, urine, or oral fluid, whereas others tolerate low to moderate *per se* Δ^9-THC concentrations in blood) (Wong et al., 2014), and public health advice regarding how long an individual should wait following cannabis use before operating a motor vehicle, limited. Currently, the Canadian 'Lower Risk Cannabis Use Guidelines' (endorsed by the Public Health Agency of Canada) recommend waiting at least 6 -hs following cannabis use before driving (Health Canada, 2019), while expert advice provided on the not-for-profit organisation 'Mothers Against Drunk Driving' (MADD Canada) website suggests waiting a minimum of 4–6 -hs (MADD Canada, 2019). Recent reports also indicate that the behaviour of cannabis users with respect to delaying driving is variable; with 13–50 % of individuals admitting to driving within 3 -hs of cannabis use in recent surveys from the United States, Canada and Australia (Arkell et al., 2020a; Bonar et al., 2019; DiGuiseppi et al., 2019; Rotermann, 2020).

Accordingly, the current systematic review summarised evidence from recent studies investigating the acute effects of Δ^9-THC on car driving performance and discrete cognitive skills related to car driving. Meta-analytic techniques were then used to estimate the magnitude and duration of Δ^9-THC-induced impairment. As the pharmacokinetic profiles of oral and inhaled (i.e. smoked, vaporised) Δ^9-THC differ substantially (Spindle et al., 2019; Vandrey et al., 2017), these different routes of administration were investigated in separate analyses as were the effects of Δ^9-THC in regular and 'other' (mostly occasional) cannabis users.

2. Methods

The methods of this systematic review are reported in accordance with the PRISMA-P 2015 Statement (Moher et al., 2015).

2.1. Literature search

Studies were identified by searching the online databases Web of Science (Thomas Reuters) and Scopus from the year 2000 until April 2020 using the Boolean expression: (cogniti* OR driving OR drive OR "processing speed" OR "reaction time" OR vigilance OR "executive function" OR memory OR psychomotor OR tracking OR perception) AND (cannabinoid* OR cannabis OR marijuana OR tetrahydrocannabinol OR THC OR nabiximols OR Sativex OR dronabinol OR marinol OR namisol). The star symbol (*) was used to capture derivatives of search terms (by suffixation) and enclosed quotation marks were used to capture exact phrases. The search was then refined by 'Document Type' (article, only) and 'Language' (English, only), if permitted by the database. Given the large number of terms that could potentially be used to retrieve relevant studies on cognitive function, and the large number of texts identified (>8000; Supplementary File 1), the authors performed a modified secondary search. This search included 15 of the 21 original terms (ensuring adequate overlap; i.e. retrieving 76 % of the records identified in the primary search), but used the terms "information processing", attention and "crystallised intelligence" instead of "processing speed", drive, perception, vigilance, psychomotor and tracking to maximise breadth.

Two investigators (D.M. & T.R.A.) independently screened the titles and abstracts against the following criteria: (1) English language; (2) full-length article; (3) original research; and (4) controlled trial in which Δ^9-THC was administered. Suitable records were then screened for eligibility by full text (see Sect. 2.2 'Eligibility Criteria'). The final decision to include (or discard) a study was made between these two investigators and discrepancies were resolved in consultation with a third investigator (I.S.M.). One investigator (D.M.) also hand-searched the reference lists of two previous systematic reviews (Broyd et al., 2016; Oomen et al., 2018) to ensure all relevant articles were captured.

2.2. Eligibility criteria

Studies that measured either simulated or on-road car driving performance, or a discrete cognitive skill related to car driving (see Sect. 2.3 'Performance Outcomes'), $\leq$12 h following a single, acute dose of Δ^9-THC in a placebo-controlled (within- or between-subject) experimental trial were eligible for inclusion. Only full-length, English-language, original research articles were accepted; all other documents were discarded.

Studies were excluded if: (1) Δ^9-THC was administered in combination with another treatment (this did not include placebo treatments, other cannabinoids or cannabis constituents, tobacco or participants' usual medication); (2) more than one dose of Δ^9-THC was administered prior to the performance test(s) during the study session; (3) either the dose of Δ^9-THC administered, or the length of time between Δ^9-THC administration and the performance test(s), was not reported and could not be estimated (e.g. in regard to dose, reporting the number of 'puffs' smoked from a cannabis cigarette was not considered adequate to estimate dose) (see Sect. 2.5' Data Extraction'); (4) results were reported in another included paper; or (5) results were not adequately reported; at a minimum studies had to report either mean performance scores or the results of relevant statistical comparisons (descriptively) (e.g. paired analyses or complex comparisons within which the effect of Δ^9-THC could be isolated; see Sect. 2.6.2 'Qualitative Synthesis'). Studies that reported sufficient data to facilitate the computation of independent-groups Hedges' *g* effect estimates were eligible for quantitative synthesis. If these data were not reported and the study was published within the previous 10 years (2010–2020), the corresponding author was contacted via email in an attempt to retrieve it. Where data were presented in graphical format only, a web-based tool (see: WebPlotDigitizer; https://apps.automeris.io/wpd/) was used to extract numeric values. 'Peak', 'minimum' and 'maximum' performance scores and scores that were averaged across Δ^9-THC and non-Δ^9-THC treatments (e.g. alcohol) were ineligible for review; performance scores that were averaged across time (i.e. > 1 h apart) or across multiple Δ^9-THC treatments were eligible for qualitative synthesis only (unless the corresponding author could provide the required data).

If a study contained multiple "intervention-arms", where more than one was eligible for inclusion, the separate "arms" were treated as discrete 'studies', termed trials (identifiable by the additional letters (e.g. a–d) in the citation). As single trials often measured serial performance (i.e., multiple times across the trial) and/or used several tasks that generated multiple outcomes, each one could contribute multiple effect estimates to the review. (Nb. Multilevel models were used to account for dependency of effect estimates in statistical analyses (Assink and Wibbelink, 2016) (see sect. 2.6.3 'Quantitative Synthesis')).

Table 1
Driving-related cognitive performance tests.

- **Divided Attention**
  - DAT (Secondary Target Identification Task)
    - DAT (Primary Mental Arithmetic Task)
    - Multi-attribute Task (Secondary Target Identification Task)
- **Tracking Performance**
  - Critical Tracking Task
    - DAT (Primary Tracking Task)
    - Multi-attribute Task (Primary Tracking Task)
    - Pursuit Tracking Task
    - Rotor Pursuit Task
    - Unstable Tracking Task
- **Information Processing**
  - Digit Cancellation Task
    - Digit Symbol Substitution Task
    - Road Sign Search Task
    - Trail Making Task (Part A)
- **Executive Function**
  - ***Conflict Control:**
    - Flanker Task
    - Go/No Go Task
    - Matching Familiar Figures Task
    - Stop Signal Task
    - Stroop Word-Colour Association Task
    - Attention Switch Task
    - Wisconsin Card Sorting Task
  - **Fluid Intelligence:**
    - Baddeley Reasoning Task
    - Stockings of Cambridge
    - Tower of London Task
- **Reaction Time**
  - Choice Reaction Time Task
    - Simple Reaction Time Task
    - Vienna Reaction Time Task
- **Motor Function**
  - **Fine Motor Function:**
    - Gibson Spiral Maze Task
    - Grooved Pegboard Task
    - Finger Tapping Task
    - Paced Finger Tapping Task
    - Secondary Finger Tapping Task
    - Smooth Pursuit Eye Movements
    - Saccadic Eye Movements
  - **Gross Motor Function:**
    - Motor Screening Task
    - Static (2-Leg) Balance
    - Dynamic Balance
- **Perception**
  - **Sensory Discrimination:**
    - 3D Structure from Motion Task
    - Auditory Oddball Detection Task
    - Dichotic Listening Task
    - Distance Estimation
    - Useful Field of View Task
    - Visual Oddball Detection Task
  - **Time Perception:**
    - Time Estimation
    - Time Reproduction
    - Self-Paced Counting Task
    - Self-Paced Finger Tapping Task
- **Sustained Attention**
  - Continuous Performance Test
    - Distracted Continuous Performance Test
    - Psychomotor Vigilance Task
    - Rapid Visual Information Processing Task
    - Sustained Attention Task
    - Signal Detection Task
    - Visual Selective Attention task
- **Working Memory**
  - Digit Span (Backward)
    - Trail Making Task (Part B)
    - *N-Back Task
    - Paced Auditory Serial Addition Task
    - Spatial N-Back Task
    - Serial Sevens Subtraction
    - Spatial Working Memory Task
    - Sternberg Memory Task
    - Verbal Fluency Task (Errors)

A description of each task and its associated outcomes can be found in Supplementary File 2. *"Non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks were analysed in the Reaction Time domain (see Sect. 2.6.3 'Quantitative Synthesis').

2.3. Performance outcomes

Studies were required to have measured either car driving performance, or a discrete cognitive "skill" related to car driving. The following "skills" (hereafter referred to as *Performance Domains*) were accepted as per Moskowitz and Fiorentino (2000): (1) Divided Attention; (2) Tracking Performance; (3) Information Processing; (4) Executive Function (subcategorised as Conflict Control and Fluid Intelligence); (5) Reaction Time; (6) Motor Function (subcategorised as Fine and Gross Motor Function); (7) Perception (subcategorised as Sensory Discrimination and Time Perception); (8) Sustained Attention; and (9) Working Memory. Measures of car driving performance were likewise subcategorised as 'Lateral Control' (outcomes included standard deviation of lane position [SDLP], lane crossings, steering deviations, maximum lateral acceleration and time out of lane), 'SDLP (Only)' (since this is often recognised as the most sensitive measure of driving impairment (Irwin et al., 2017; Verster and Roth, 2011)), 'Speed', 'Speed Variability', 'Car Following (CF) Headway' (outcomes included CF headway and gain),' CF Headway Variability' (outcomes included CF headway variability and coherence), 'Reaction Time', and 'Other'.

Each driving-related cognitive performance test used in the included studies was categorised into one of the above Performance Domains (Table 1). Tests that were not considered indicative of a driving-related skill (or those based on subjective assessment, e.g. field sobriety tests) were excluded. While the majority of outcomes measured on eligible performance tests were included in this review, a small number were excluded for various reasons (e.g. reaction time on incorrect trials was considered unsuitable as no single direction of change (i.e. an increase or decrease) is consistently indicative of 'impairment'). In addition, if an outcome could be broken down into multiple "sub-outcomes" (e.g. both the total and individual number of within- and between-search errors on a working memory task), and all measures were reported, only the sub-outcomes were included. All excluded tasks and excluded outcomes (with reasons for exclusion) are listed in Supplementary File 2.

2.4. Quality assessment

The methodological quality of included studies was assessed using the Rosendal scale (see Table II in Van Rosendal et al. (2010)). This scale, which combines the Jadad scoring system (Jadad et al., 1996), PEDro scale (Maher et al., 2008), and Delphi List (Verhagen et al., 1998), assesses a number of factors associated with the minimization of experimental bias (e.g. blinding, participant selection, randomisation, data reporting). Excellent methodological quality is indicated by a Rosendal Score $\geq$60 % (Jadad et al., 1996). Rosendal scores were calculated by dividing the total number of 'Yes' responses by the total number of applicable items. Studies were ineligible for quantitative synthesis (but included in the qualitative synthesis) if they received a Rosendal score $<$50 %.

2.5. Data extraction

Data were extracted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* Checklist of Items to Consider in Data Collection for Data Extraction (Chandler et al., 2019). Extracted data included: (1) the study design; (2) participant characteristics (e.g. age, body weight, sex, cannabis use behaviour); (3) treatment characteristics (e.g. type, composition, route of administration, dose); (4) performance test characteristics (e.g. procedure, number of assessments, the length of time between Δ^9-THC administration and the performance test(s)), and;

Table 2
Terms used to describe participants' cannabis use behaviour.

Population	Definition
Cannabis Naïve	No lifetime exposure
Current Non-Users	No use ≥1 month and ≥1 lifetime exposure
Infrequent Users	<1 use per month and ≥1 lifetime exposure
Monthly Users	1 to <4 uses per month
Weekly Users	1 to <4 uses per week
Daily Users	≥4 uses per week
Unclear	Insufficient information provided

See Sect. 2.5 'Data Extraction' for full details. For analytical purposes, those trials in which all participants used cannabis weekly or more often were considered to involve "Regular Users"; all other trials were considered studies of "Other Uses".

(5) blood Δ^9-THC and 11-OH-Δ^9-THC concentrations as well as subjective ratings of intoxication at the time of performance testing (where available). (Nb. The latter were included for descriptive purposes only and were not formally analysed).

The following methods should be noted:

If a study administered the same performance test more than once within a one-hour period, only one of these assessments was included. In each case, the assessment that took place *first* within the hour; or, if more than two assessments were completed, the assessment that would result in the greatest loss of data (i.e. the exclusion of more assessments), was omitted to reduce data dependency.

The *Post-Treatment Time Interval* was typically estimated as the total length of time between Δ^9-THC administration and the beginning of the performance test (or cognitive battery, if multiple tasks were performed and the start time of individual tasks was not reported). However, if the test (or battery) took >10 min to complete, it was taken as the length of time to the 'mid-way' point of the assessment. If the exact timing of the assessment was not reported, but it clearly took place shortly following Δ^9-THC administration, the interval was approximated as 15 min. Tests were assumed to last ≤10 min unless otherwise stated.

The terms used to describe participants' *Cannabis Use Behaviour* are defined in Table 2. Each population was categorised based on the range of use behaviours exhibited by its participants (e.g., if participants used cannabis on between 2–16 days [or between 2–16 times] within the last 3 months, the population were termed [on average] 'Infrequent–Weekly Users'). If only the Mean ± SD number of uses was reported, the range was estimated as ±3SDs from the mean. However, if the lower limit was <0 (or if the SD was not reported), the behaviour of the population was considered 'Unclear'. The population's Cannabis Use Behaviour was also considered 'Unclear' if only > *x* or < *x* uses was reported, unless the reported value was ≥1 use (or more) per week (i.e. Weekly–Daily Users or Daily Users, as appropriate) or ≤4 uses (or less) per month (i.e. Infrequent–Monthly Users or Infrequent Users, as appropriate). These terms were developed for descriptive purposes only. When Cannabis Use Behaviour was included as a covariate in the meta-regression analyses (see Sect.2.6.3b 'Meta-Regression Analysis'), these categories were collapsed into two groups: '*Regular Cannabis Users*' (which included populations of Daily Users, Weekly Users and Weekly–Daily Users) and '*Other Cannabis Users*' (all other populations).

2.6. Data synthesis

2.6.1. Hedges' g effect estimates

Hedges' *g* intervention effect estimates were calculated by standardising the mean difference between control (placebo) and intervention (Δ^9-THC) performance scores against either the SD of the performance change (SD_Δ) (if a within-subject design was used) or the pooled SD (SD_{pooled}) (if a between-subject design was used) and correcting for bias due to small sample size (where sufficient data were reported) (Borenstein et al., 2011). The magnitude of effect was then defined in accordance with Cohen (1988), where Hedges' *g* values of approximately ≤0.2 (range: <0.00–0.39), 0.5 (range: 0.40–0.79), and ≥0.8 were considered small, medium and large, respectively. Negative effect estimates were used to signify an impairing effect of Δ^9-THC, irrespective of the performance outcome.

Unless either raw data, the SD_Δ, or a *p*-value (or *t*-statistic) derived from a paired *t*-test was reported (or provided), the SD_Δ was estimated using the formula indicated below (Chandler et al., 2019):

$$SD_\Delta = \sqrt{\left(SD^2_{Placebo} + SD^2_{\Delta 9\text{-THC}}\right) - \left(2 \times R \times SD_{Placebo} \times SD_{\Delta 9\text{-THC}}\right)} \quad (1)$$

where *R* is the correlation coefficient. *R* was approximated as the mean correlation coefficient ($R = 0.530$) calculated using raw performance data from 16 trials (Arkell et al., 2019; Ballard and de Wit, 2011; Brown et al., 2019; Pabon and de Wit, 2019; Schlienz et al., 2020; Spindle et al., 2020, 2018) and 18 *p*-values derived from paired *t*-tests (Bhattacharyya et al., 2015; Morrison et al., 2009; van den Elsen et al., 2017). Where these Hedges' *g* effect estimates were meta-analysed (see Sect. 2.6.3 'Quantitative Synthesis'), the meta-analyses were repeated using values calculated at $R = 0.2$ and $R = 0.8$ to examine their robustness to the imputed *R*.

Where a *t*-statistic derived from a paired *t*-test was reported, the formula indicated below was used to calculate the the SD_Δ (Chandler et al., 2019):

$$SD_\Delta = \frac{\text{Mean Difference}}{t\text{-statistic}} \times \sqrt{n} \quad (2)$$

where *n* is the sample size. If a *p*-value (i.e. $p = x$ or $p < x$) derived from a paired *t*-test was reported, it was used to derive a *t*-statistic to substitute into this equation.

The SD_{pooled} was calculated using the formula indicated below (Chandler et al., 2019):

$$SD_{pooled} = \sqrt{\frac{\left(SD^2_{Placebo} + SD^2_{\Delta 9\text{-THC}}\right)}{2}} \quad (3)$$

The above calculations were performed using median performance scores (instead of mean) if this was all that was reported. If required, missing SDs were estimated from 95 % confidence intervals (CIs), standard error (SE) values, and interquartile ranges as described by Chandler et al. (2019).

2.6.2. Qualitative synthesis

Results were synthesised qualitatively if an effect estimate: (a) could not be calculated (but mean performance scores or the results of relevant statistical comparisons were reported; see Sect. 2.2 'Eligibility Criteria'); or (b) could be calculated but was not eligible for quantitative synthesis (see Sect. 2.6.3 'Quantitative Synthesis'). If an effect estimate could not be calculated, results were described in terms of whether Δ^9-THC was reported to have had a statistically significant effect ($p < 0.05$) on the outcome of interest. However, if this information was unavailable, the direction of the mean change was reported. If an outcome was analysed within a complex model (e.g. including more than two treatments and/or other factors, e.g. time), and no main effect of treatment or relevant interactions were observed, the comparison of interest was assumed to be non-significant. If a main effect of treatment or relevant interaction was observed, significance was determined on the basis of post hoc comparisons. If these comparisons were not performed, or there was any ambiguity in the reported result, the statistical significance was not reported (i.e. the direction of the mean change was reported or, if this was unavailable, the outcome was considered ineligible for inclusion).

2.6.3. Quantitative synthesis

An outcome was eligible for quantitative synthesis if: (a) an effect estimate could be calculated; and (b) it was not derived from a study of a clinical population (as the medical conditions studied were considered too heterogenous to consolidate into a meaningful analysis) or a study

that scored <50 % on the Rosendal scale. The quantitative synthesis comprised of a series of four-level meta-analyses and four-level meta-regression analyses with multiple random effects (Assink and Wibbelink, 2016). A two-level analysis is equivalent to a traditional random effects analysis in which there is only one random effect. We added random effects at two additional levels to account for dependency among effect estimates derived from: (1) the same studies; and (2) the same trials. The four sources of variance modelled were therefore: (Level 1) the sampling variance for the observed effect estimates; (Level 2) the variance between effect estimates derived from the same studies; (Level 3) the variance between effect estimates derived from different trials in the same studies, and; (Level 4) the variance between studies. All statistical analyses were performed using R (version 4.0.1) with the metafor-package, using syntax adapted from Assink and Wibbelink (2016). The accompanying R scripts are available in Supplementary File 7. Effect estimates were weighted by the inverse variance of the performance change and statistical significance was attained if the 95 % CI did not include zero. Heterogeneity was assessed using Cochran's Q, the I^2-index and the within-cluster and between-cluster variance components (i.e. σ_1^2, σ_2^2 and σ_3^2). Significant heterogeneity was indicated by a *p*-value <0.05 for Cochran's Q (Borenstein et al., 2011). Data are reported as Mean ± SD, unless otherwise stated. Note that although they are presented in the Executive Function and Working Memory domains, "non-conflict" outcomes (e.g., Go Reaction Time, Non-Switch Reaction Time, Congruent Reaction Time) and outcomes measured on '0-Back' Tasks were analysed in the Reaction Time domain due to their relative simplicity.

2.6.3.1. Meta-Analysis. Meta-analyses were initially performed to gain a general understanding of Δ^9-THC's acute (or "peak") effects on car driving performance (see Sect. 2.3 'Performance Outcomes'). Only those outcomes measured "shortly" post-treatment (or, if Δ^9-THC was administered orally, when blood Δ^9-THC/11-OH-Δ^9-THC concentrations and subjective feelings of intoxication were expected to be elevated (Schlienz et al., 2020)); that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously, or between 1.5 and 3.5 h of oral Δ^9-THC administration, were included in these analyses.

2.6.3.2. Meta-regression analysis. Restricted maximum likelihood multiple meta-regression analyses were performed to generate models that facilitate estimation of the duration of Δ^9-THC-induced cognitive impairment; in other words, the time it takes for an individual to "recover" (i.e. have their cognitive abilities return to baseline or a level at which Δ^9-THC's effects are no longer meaningful) following acute Δ^9-THC administration. Given the differences in their pharmacokinetic profiles (Spindle et al., 2019; Vandrey et al., 2017)], the effects of orally administered and inhaled (i.e. smoked or vaporised) Δ^9-THC were investigated in separate models. Effect estimates derived from trials that administered Δ^9-THC intravenously were not analysed as data were limited and (although this route of administration produces a similar pharmacokinetic profile to inhaled Δ^9-THC (Ohlsson et al., 1980)) the doses administered via this route were not comparable to others. The following covariates were included in each model as applicable: Performance Domain (see Sect. 2.3 'Performance Outcomes'), Cannabis Use Behaviour (Regular vs. Other Cannabis Users; see Sect. 2.5 'Data Extraction'), Δ^9-THC Dose, Route of Administration, and Post-Treatment Time Interval (see Sect. 2.5 'Data Extraction'). Post-Treatment Time Interval was also included as a curvilinear (quadratic) factor in the analysis of oral Δ^9-THC effects (following inspection of scatterplots). Performance Domains that did not indicate significant impairment in the initial meta-analyses of "peak" Δ^9-THC effects or that contained a limited amount of data (<10 effect estimates) were not analysed. The 'SDLP (Only)' domain was included in place of the 'Lateral Control' domain to aid interpretation, since drug-induced changes in SDLP have been well-researched (Dassanayake et al., 2011; Irwin et al., 2017). The Post-Treatment Time Interval covariate was centred (i.e. rescaled to have a mean of zero) in the analysis of oral Δ^9-THC effects to ensure values were not correlated with the quadratic computations. Categorical variables were dummy transformed with m – 1, where m is the number of levels of the original variable. Goodness of fit was approximated using the pseudo-R^2 value as standard R^2 values cannot be derived for multi-level meta-regression models (Nakagawa and Schielzeth, 2013). Unlike the standard value, the pseudo-R^2 does not provide an 'absolute' quantification of model fit, rather, an indication of how much better the full model is once the moderators have been incorporated.

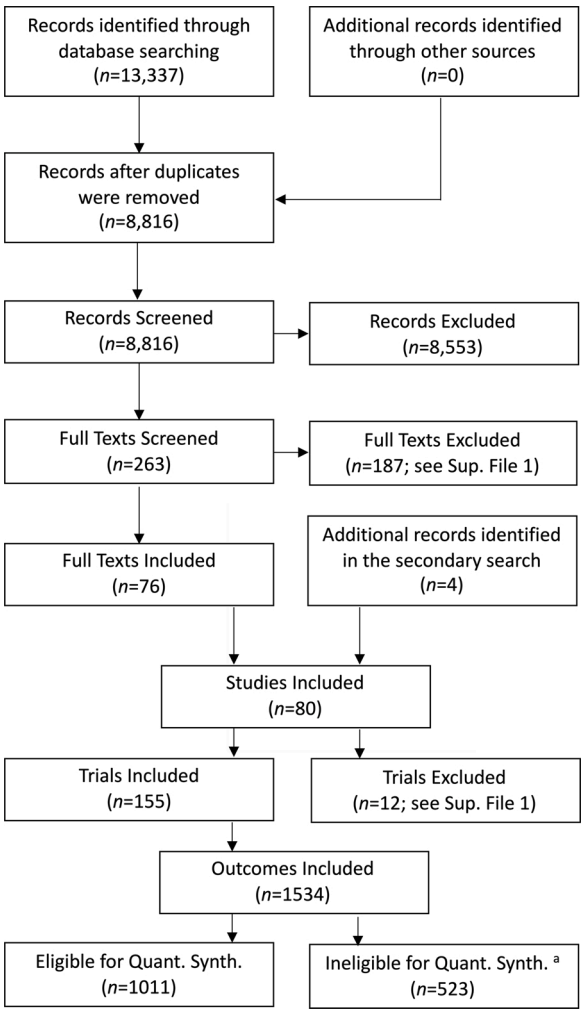


Fig. 1. Shortened PRISMA Flow Diagram. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations, or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis. The term 'trial' is defined in Sect. 2.2 'Eligibility Criteria'. A full PRISMA Flow Diagram can be found in Supplementary File 1).

3. Results

3.1. Overview of included studies and study quality

155 trials ($n = 3454$ participants; 71 % male) derived from 80 original research studies were included in this systematic review. Details of the study selection process are available in Supplementary File 1 and summarised in Fig. 1. The methodological quality assessment yielded a Mean ± SD Rosendal score of 62 ± 10 % (43–93 %) (see Supplementary File 3); six studies scored <50 % and were therefore ineligible for

Table 3
Summary of all included outcomes and trials.

	Total (*n*)			Eligible for Quantitative Synthesis (*n*)			Ineligible for Quantitative Synthesis [a] (*n*)		
	Outcomes	Trials	Participants	Outcomes	Trials	Participants	Outcomes	Trials	Participants
Total:	1534	155	3454 (71 % M)	1011	108	2583 (72 % M)	523	73	1497 (69 % M)
Cognitive Functions:									
Divided Attention	166	26	510 (70 % M)	148	23	486 (72 % M)	18	3	24 (50 % M)
Tracking Performance	137	31	646 (72 % M)	122	27	606 (66 % M)	15	7	87 (74 % M)
Information Processing	205	27	473 (65 % M)	128	16	290 (61 % M)	77	11	183 (72 % M)
Conflict Control	97	31	899 (79 % M)	59	27	805 (81 % M)	38	15	370 (71 % M)
Fluid Intelligence	70	16	448 (76 % M)	22	10	346 (80 % M)	48	8	154 (69 % M)
[b] Reaction Time	110	39	846 (67 % M)	49	28	647 (68 % M)	61	16	279 (68 % M)
Fine Motor Function	56	14	334 (59 % M)	52	12	310 (60 % M)	4	2	24 (50 % M)
Gross Motor Function	17	6	110 (46 % M)	5	3	74 (43 % M)	12	3	36 (50 % M)
Sensory Discrimination	25	10	201 (67 % M)	12	5	67 (88 % M)	13	6	149 (60 % M)
Time Perception	48	16	376 (60 % M)	16	6	150 (53 % M)	32	10	226 (65 % M)
Sustained Attention	114	35	751 (75 % M)	67	26	524 (81 % M)	47	14	321 (65 % M)
Working Memory	264	44	974 (70 %)	222	38	800 (71 % M)	42	12	363 (67 % M)
Car Driving:									
Lateral Control	65	23	438 (71 % M)	39	18	378 (71 % M)	26	5	60 (70 % M)
SDLP (Only)	32	19	389 (67 % M)	28	17	353 (69 % M)	4	2	36 (50 % M)
Speed	17	12	237 (69 % M)	17	12	237 (69 % M)	0	–	–
Speed Variability	13	10	112 (63 % M)	13	10	112 (63 % M)	0	–	–
CF Headway	16	10	160 (60 % M)	12	8	124 (63 % M)	4	2	36 (50 % M)
CF Headway Variability	16	10	160 (60 % M)	12	8	124 (63 % M)	4	2	36 (50 % M)
Reaction Time	14	10	160 (59 % M)	10	8	124 (61 % M)	4	2	36 (50 % M)
Other	6	2	65 (88 % M)	6	2	65 (88 % M)	0	–	–
Clinical Populations:	78	11	204 (70 % M)	–	–	–	78	11	204 (70 % M)

CF: Car Following; M: Males; SDLP: Standard Deviation of Lane Position. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis (qualitative synthesis only); *b*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Trials that include a combination of eligible and ineligible outcomes are presented in both relevant categories. Trials that did not report the sex of their participants were omitted when calculating the proportion of males.

Table 4
Key characteristics of all included trials.

	Trials (*n*)	Studies (*n*)	Outcomes (*n*)		Route of Administration (*n* Outcomes)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Outcomes)	
								Regular	Other
All Trials	155	80	1534	Oral:	578	16 ± 13	234 ± 164	32	546
				Vaporised:	344	14 ± 8	153 ± 132	63	281
				Smoked:	478	30 ± 20	137 ± 133	87	391
				Intravenous:	134	2.6 ± 1.3	48 ± 61	21	113
Trials Eligible for Quantitative Synthesis	108	58	1011	Oral:	307	20 ± 15	222 ± 148	12	295
				Vaporised:	305	14 ± 8	158 ± 137	57	248
				Smoked:	331	32 ± 22	139 ± 129	46	285
				Intravenous:	68	2.5 ± 1.3	28 ± 10	1	67
Trials Ineligible for Quantitative Synthesis [a]	73	38	523	Oral:	271	13 ± 9	248 ± 183	20	251
				Vaporised:	39	14 ± 9	111 ± 78	6	33
				Smoked:	147	23 ± 7	129 ± 140	41	106
				Intravenous:	66	2.7 ± 1.2	67 ± 82	20	46

Tx: Treatment. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis. Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. Trials that include a combination of eligible and ineligible outcomes are presented in both relevant categories.

quantitative synthesis. Overall, the included trials measured a total of 1534 relevant outcomes; 1011 of which were eligible for quantitative synthesis. The number of outcomes included in each individual Performance Domain is presented in Table 3; characteristics of all included trials and those eligible for quantitative synthesis are summarised in Tables 4 and 5, respectively. A detailed qualitative synthesis is available in Supplementary File 4.

3.2. Meta-Analyses of "peak" Δ^9-THC effects

The characteristics of trials eligible for meta-analyses (see Sect. 2.6.3a 'Meta-Analysis') are summarised in Table 6; with results of the meta-analyses summarised in Table 7. The results of the analyses completed using different correlation coefficients ($R = 0.2$ and 0.8) are available in Supplementary File 5.

3.2.1. Cognitive performance

Meta-analyses revealed significant detrimental effects of Δ^9-THC on Divided Attention, Tracking Performance, Information Processing, Conflict Control, Fluid Intelligence, Reaction Time, Fine Motor Function, Sustained Attention and Working Memory (Table 7). Neither Sensory Discrimination nor Time Perception demonstrated significant impairment. Gross Motor Function was not subject to meta-analysis due to the limited amount of available data.

Table 5
Key characteristics of trials that were eligible for quantitative synthesis.

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Cognitive Functions:								
Divided Attention	23	148	*Oral:	42	28 ± 17	249 ± 136	0	42
			*Vaporised:	59	14 ± 8	200 ± 142	5	54
			*Smoked:	47	20 ± 11	203 ± 149	4	43
			Intravenous:	0	–	–	–	–
Tracking Performance	27	122	*Oral:	33	25 ± 15	275 ± 181	0	33
			*Vaporised:	39	15 ± 8	163 ± 142	8	31
			*Smoked:	50	30 ± 16	188 ± 42	7	43
			Intravenous:	0	–	–	–	–
Information Processing	16	128	*Oral:	46	27 ± 17	268 ± 158	0	46
			*Vaporised:	50	13 ± 8	226 ± 139	0	50
			*Smoked:	32	25 ± 22	225 ± 142	4	28
			Intravenous:	0	–	–	–	–
Conflict Control	27	59	*Oral:	11	10 ± 2	94 ± 5	0	0
			*Vaporised:	24	17 ± 6	34 ± 9	16	0
			*Smoked:	24	28 ± 13	93 ± 97	3	21
			Intravenous:	0	–	–	–	–
Fluid Intelligence	10	22	Oral:	0	–	–	–	–
			*Vaporised:	14	21 ± 0	51 ± 10	13	1
			*Smoked:	6	27 ± 10	165 ± 142	0	6
			Intravenous:	2	2.3 ± 0.3	40 ± 14	0	2
Reaction Time	28[a]	49[a]	*Oral:	18	11 ± 3	108 ± 24	0	18
			*Vaporised:	6	17 ± 7	30 ± 9	5	1
			*Smoked:	23	36 ± 23	88 ± 98	2	21
			Intravenous:	2	1.3 ± 0.0	30 ± 0	0	2
Fine Motor Function	12	52	*Oral:	32	6 ± 5	154 ± 80	0	32
			Vaporised:	0	–	–	–	–
			Smoked:	4	80 ± 7	60 ± 0	4	0
			Intravenous:	16	1.6 ± 0.5	20 ± 0	0	16
Gross Motor Function	3	5	Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	0	–	–	–	–
			Intravenous:	5	1.7 ± 0.5	20 ± 0	0	5
Sensory Discrimination	5	12	Oral:	10	10 ± 0	90 ± 0	0	10
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Time Perception	6	16	Oral:	14	11 ± 4	106 ± 9	0	14
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Sustained Attention	26	67	*Oral:	11	11 ± 4	382 ± 213	0	11
			*Vaporised:	6	21 ± 0	20 ± 12	2	4
			*Smoked:	31	59 ± 20	106 ± 37	10	21
			Intravenous:	19	3.4 ± 1.2	32 ± 11	0	19
Working Memory	38	222	*Oral:	50	25 ± 17	242 ± 127	0	50
			*Vaporised:	72	11 ± 7	176 ± 139	8	64
			*Smoked:	76	32 ± 21	123 ± 127	0	76
			Intravenous:	24	2.8 ± 1.3	30 ± 10	1	23
Car Driving:								
Lateral Control	18	39	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	19	19 ± 8	107 ± 70	0	19
			Smoked:	12	41 ± 33	37 ± 9	4	8
			Intravenous:	0	–	–	–	–
SDLP (Only)	17	28	Oral:	8	15 ± 5	203 ± 42	2	6
			*Vaporised:	13	18 ± 7	117 ± 79	0	13
			*Smoked:	7	55 ± 36	36 ± 8	4	3
			Intravenous:	0	–	–	–	–
Speed	12	17	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	9	47 ± 36	34 ± 9	4	5
			Intravenous:	0	–	–	–	–
Speed Variability	10	13	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	5	18 ± 5	37 ± 11	0	5
			Intravenous:	0	–	–	–	–
CF Headway	8	12	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
CF Headway Variability	8	12	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	4	14 ± 0	135 ± 104	0	4

(*continued on next page*)

Table 5 (*continued*)

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Reaction Time	8	10	Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
			Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	0	–	–	–	–
Other	2	6	Smoked:	2	15 ± 3	45 ± 0	0	2
			Intravenous:	0	–	–	–	–
			Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	6	9 ± 7	38 ± 6	0	6
			Intravenous:	0	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position; Tx: Treatment. *Included in a meta-regression analysis. *a*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. A description of each cognitive task can be found in Supplementary File 2.

3.2.2. Car driving performance

Meta-analyses revealed significant detrimental effects of Δ^9-THC on Lateral Control, SDLP (Only) and Reaction Time (Table 7). Neither CF Headway, CF Headway Variability, Speed, nor Speed Variability were significantly influenced by Δ^9-THC. 'Other Outcomes' were not analysed due to the limited amount of available data.

3.3. Estimated duration of Δ^9-THC effects

The characteristics of trials eligible for meta-regression analysis (see Sect. 2.6.3a 'Meta-Regression') are summarised in Table 5; with results of the meta-regression analyses summarised in Table 8. The results of the analyses completed using different correlation coefficients ($R = 0.2$ and 0.8) are available in Supplementary File 5.

3.3.1. Smoked and vaporised Δ^9-THC

Effect estimates derived from trials that administered Δ^9-THC via smoking or vaporisation were included in the multiple meta-regression analyses of inhaled Δ^9-THC effects. The covariates included in each analysis are listed in Table 8.

An initial (combined) analysis of Regular and Other Cannabis Users included 579 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 3.7–94 mg (Interquartile Range [IQR]: 10–26 mg) and 1–480 min (IQR: 45–240 min) respectively. The following covariates were significantly related to effect size: Performance Domain, Cannabis Use Behaviour, Route of Administration, Δ^9-THC Dose and Post-Treatment Time Interval (p's<0.050; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased and less negative as the Post-Treatment Time Interval increased. It also differed across the Performance Domains. Regular Cannabis Use and Smoking were associated with less impairment (i.e., less negative Hedges' g effect estimates) than Other Cannabis Use and Vaporisation, respectively. However, the model retained a significant amount of unexplained heterogeneity ($p < 0.001$; pseudo-$R^2 = 0.0$) and the omission of outcomes derived from trials of Regular Cannabis Users strengthened it substantially (pseudo-$R^2 = 0.64$). Thus, the initial (combined) analysis of Regular and Other Cannabis Users may be limited in its ability to simultaneously describe inhaled Δ^9-THC's effects in these populations. Separate analyses were therefore also performed for Regular and Other Cannabis Users.

The subsequent analysis of Regular Cannabis Users included 59 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 5.5–86 mg (IQR: 21–26 mg) and 20–440 min (IQR: 40–60 min), respectively. None of the covariates included were significantly related to effect estimate (p's>0.050; pseudo-$R^2 = 0.0$; Table 8). It was therefore unsuitable to predict the magnitude and duration of inhaled Δ^9-THC's cognitive effects in this population.

The subsequent analysis of Other Cannabis Users included 481 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 3.7–69 mg (IQR: 10–25 mg) and 1–480 min (IQR: 60–240 min) respectively. The following covariates were significantly related to effect size: Performance Domain, Δ^9-THC Dose and Post-Treatment Time Interval (p's<0.05; pseudo-$R^2 = 0.64$; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased and less negative as the Post-Treatment Time Interval increased. It also decreased across the following Performance Domains (ordered from least to most sensitive to inhaled Δ^9-THC effects): Sustained Attention, Conflict Control, Reaction Time, Working Memory, Divided Attention, Tracking Performance, SDLP (Only) and Information Processing. The duration of inhaled Δ^9-THC's cognitive effects (based on the model presented in Table 8) are predicted in Table 9 and graphed in Fig. 2 (Nb. Tracking Performance is used as an example in this Figure; the average duration across all aggregated Performance Domains is graphed in Supplementary File 8). Values can also be imputed using the spreadsheet presented in Supplementary File 6.

3.3.2. Oral Δ^9-THC

The following covariates were included in the multiple meta-regression analysis of oral Δ^9-THC effects: Performance Domain, Post-Treatment Time Interval (linear and curvilinear) and Δ^9-THC Dose. Cannabis Use Behaviour was not included as a covariate as all outcomes were derived from trials of Other Cannabis Users. The resulting model included 243 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 2.5–50 mg (IQR: 10–25 mg) and 60–720 min (IQR: 120–360 min), respectively. Three of the four covariates were significantly related to effect size (p's<0.050, pseudo-$R^2 = 0.28$; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased. It also decreased across the following Performance Domains (i.e. ordered from least to most sensitive to oral Δ^9-THC effects): Working Memory, Sustained Attention, Divided Attention, Fine Motor Function, Reaction Time, Information Processing, Tracking Performance, and Conflict Control. The curvilinear component of the relationship between Hedges' g and the Post-Treatment Time Interval was U shaped (i.e. indicating a delay to peak impairment and subsequent recovery). The duration of oral Δ^9-THC's cognitive effects (based on the model presented in Table 8) are predicted in Table 9 and graphed in Fig. 3 (Nb. Tracking Performance is used as an example in this Figure; the average duration across all aggregated Performance Domains is graphed in Supplementary File 8). Values can also be imputed using the spreadsheet presented in Supplementary File 6.

Table 6
Key characteristics of trials that were eligible for inclusion in meta-analyses of peak Δ^9-THC effects.

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Cognitive Functions:								
Divided Attention	22	46	Oral:	11	30 ± 17	153 ± 31	0	11
			Vaporised:	17	16 ± 7	42 ± 16	5	12
			Smoked:	17	22 ± 16	52 ± 28	1	16
			Intravenous:	0	–	–	–	–
Tracking Performance	27	49	Oral:	10	25 ± 16	150 ± 32	0	10
			Vaporised:	17	18 ± 6	41 ± 11	8	9
			Smoked:	22	40 ± 18	59 ± 22	1	21
			Intravenous:	0	–	–	–	–
Information Processing	13	31	Oral:	13	26 ± 18	146 ± 33	0	13
			Vaporised:	10	13 ± 7	44 ± 21	0	10
			Smoked:	8	49 ± 34	60 ± 0	4	4
			Intravenous:	0	–	–	–	–
Conflict Control	27	53	Oral:	11	10 ± 2	94 ± 5	0	11
			Vaporised:	24	17 ± 7	35 ± 7	16	8
			Smoked:	18	30 ± 14	49 ± 24	3	15
			Intravenous:	0	–	–	–	–
Fluid Intelligence	10	18	Oral:	0	–	–	–	–
			Vaporised:	14	21 ± 0	51 ± 10	13	1
			Smoked:	2	27 ± 13	45 ± 0	0	2
			Intravenous:	2	2.3 ± 0.3	40 ± 14	0	2
Reaction Time	24 [a]	38 [a]	Oral:	13	11 ± 3	119 ± 35	0	13
			Vaporised:	6	17 ± 7	30 ± 9	5	1
			Smoked:	17	32 ± 23	35 ± 12	2	15
			Intravenous:	2	1.3 ± 0.0	30 ± 0	0	2
Fine Motor Function	12	48	Oral:	28	6 ± 5	124 ± 11	0	28
			Vaporised:	0	–	–	–	–
			Smoked:	4	80 ± 7	60 ± 0	4	0
			Intravenous:	16	1.5 ± 0.5	20 ± 0	0	16
Gross Motor Function	3	5	Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	0	–	–	–	–
			Intravenous:	5	1.7 ± 0.5	20 ± 0	0	5
Sensory Discrimination	5	12	Oral:	10	10 ± 0	90 ± 0	0	10
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Time Perception	6	16	Oral:	14	11 ± 4	106 ± 9	0	14
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Sustained Attention	16	40	Oral:	2	15 ± 0	120 ± 0	0	2
			Vaporised:	6	21 ± 0	20 ± 12	2	4
			Smoked:	13	73 ± 17	67 ± 13	10	3
			Intravenous:	19	3.4 ± 1.2	32 ± 11	0	19
Working Memory	36	116	Oral:	14	25 ± 18	144 ± 33	0	14
			Vaporised:	26	10 ± 5	45 ± 15	8	18
			Smoked:	52	38 ± 22	51 ± 17	0	52
			Intravenous:	24	2.8 ± 1.3	30 ± 10	1	23
Car Driving:								
Lateral Control	16	28	Oral:	6	15 ± 5	180 ± 0	2	4
			Vaporised:	10	20 ± 9	51 ± 5	0	10
			Smoked:	12	41 ± 33	37 ± 9	4	8
			Intravenous:	0	–	–	–	–
SDLP (Only)	15	19	Oral:	6	15 ± 5	180 ± 0	2	4
			Vaporised:	6	17 ± 8	48 ± 5	0	6
			Smoked:	7	55 ± 36	36 ± 8	4	3
			Intravenous:	0	–	–	–	–
Speed	12	15	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	9	47 ± 36	34 ± 9	4	5
			Intravenous:	0	–	–	–	–
Speed Variability	10	11	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	5	18 ± 5	37 ± 11	0	5
			Intravenous:	0	–	–	–	–
CF Headway	8	8	Oral:	6	15 ± 6	180 ± 0	2	4
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
CF Headway Variability	8	8	Oral:	6	15 ± 6	180 ± 0	2	4

(*continued on next page*)

Table 6 (*continued*)

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Reaction Time	8	8	Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
			Oral:	6	15 ± 6	180 ± 0	2	4
Other	2	6	Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	45 ± 0	0	2
			Intravenous:	0	–	–	–	–
			Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	6	9 ± 7	38 ± 6	0	6
			Intravenous:	0	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position; Tx: Treatment. *a*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. A description of each cognitive task can be found in Supplementary File 2. Only those assessments conducted "shortly" post-treatment; that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously or between 1.5–3.5 h of oral Δ^9-THC administration were eligible for meta-analysis.

Table 7
Results of meta-analyses investigating the 'peak' effect of Δ^9-THC on car driving and related cognitive functions.

Performance Domain	Trials (n)	Effect Estimates (n)	Effect of Δ^9-THC		Heterogeneity				
			Hedges' *g* (95% CIs)	*p*-value	I^2-value	*p*-value	σ_1^2	σ_2^2	σ_3^2
Cognitive Functions:									
Divided Attention	22	46	–0.28 (–0.36, –0.20)	<0.001	14.2	0.291	<0.001	0.009	<0.001
Tracking Performance	27	49	–0.42 (–0.58, –0.25)	<0.001	64.8	0.002	<0.001	0.019	0.059
Information Processing	13	31	–0.38 (–0.55, –0.21)	<0.001	23.8	0.306	<0.001	0.002	0.021
Conflict Control	27	53	–0.34 (–0.42, –0.25)	<0.001	58.4	<0.001	0.047	<0.001	<0.001
Fluid Intelligence	10	18	–0.37 (–0.46, –0.27)	<0.001	16.6	0.283	0.005	<0.001	<0.001
Reaction Time	24	38	–0.28 (–0.43, –0.13)	<0.001	53.3	0.002	<0.001	0.009	0.047
Fine Motor Function	12	48	–0.36 (–0.60, –0.12)	0.004	61.9	<0.001	<0.001	0.026	0.048
[a]Gross Motor Function	3	5	–	–	–	–	–	–	–
Sensory Discrimination	5	12	+0.09 (–0.08, +0.25)	0.275	0.0	0.458	<0.001	<0.001	<0.001
Time Perception	6	16	–0.05 (–0.30, +0.20)	0.670	54.4	0.070	0.008	<0.001	0.028
Sustained Attention	16	40	–0.23 (–0.37, –0.10)	<0.001	20.3	0.675	<0.001	<0.001	0.019
Working Memory	36	116	–0.36 (–0.52, –0.20)	<0.001	69.6	<0.001	0.003	0.019	0.084
Car Driving:									
Lateral Control	16	28	–0.24 (–0.41, –0.08)	0.005	35.7	0.394	<0.001	<0.001	0.031
SDLP (Only)	15	19	–0.29 (–0.47, –0.11)	0.003	32.3	0.322	<0.001	<0.001	0.027
Speed	12	15	+0.14 (–0.01, +0.29)	0.061	0.0	0.636	<0.001	<0.001	<0.001
Speed Variability	10	11	–0.16 (–0.35, +0.02)	0.074	0.7	0.786	<0.001	<0.001	0.001
CF Headway	8	8	–0.03 (–0.32, +0.27)	0.843	44.4	0.085	0.021	0.023	0.005
CF Headway Variability	8	8	–0.24 (–0.58, +0.11)	0.151	37.1	0.488	<0.001	<0.001	0.038
Reaction Time	8	8	–0.47 (–0.70, –0.23)	0.002	15.7	0.230	0.007	0.005	<0.001
[a]Other	2	6	–	–	–	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position. Details of included studies are summarised in Table 6 and presented in Supplementary File 4. A description of each cognitive task can be found in Supplementary File 2. All negative effect estimates (Hedges' *g* values) indicate a detrimental effect of Δ^9-THC, irrespective of the performance outcome. Only those assessments conducted "shortly" post-treatment; that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously or between 1.5–3.5 h of oral Δ^9-THC administration were included in these analyses. *a*: Unsuitable for meta-analysis.

3.4. Δ^9-THC effects in clinical populations

Eleven trials ($n = 204$; 70 % male) derived from 6 studies investigated the cognitive effects of Δ^9-THC in clinical populations (Supplementary File 4). Four outcomes indicated significant, detrimental effects of Δ^9-THC; an additional 59 outcomes were not significantly affected, and the statistical significance of the 15 remaining comparisons were unclear. All significant detrimental effects were observed in one study that measured Gross Motor Function (Static 2-Leg Balance and Dynamic Balance) 120 min post-Δ^9-THC administration (1.5 mg, oral) in individuals with dementia. Moderate negative Hedges' *g* effect estimates were also reported in several trials that measured Sustained Attention (2.7 mg, oral; 21 mg, smoked; 2.5–5.0 mg, i.v.). However, 68 of the 78 outcomes that were measured indicated either small negative or positive Hedges' *g* effect estimates.

4. Discussion

This study addresses current safety-related concerns around the duration of impairment arising from acute consumption of oral or inhaled Δ^9-THC-containing cannabis. We systematically reviewed recent studies investigating the acute effects of Δ^9-THC on driving performance and discrete cognitive skills related to driving; meta-analytic techniques were then used to estimate the magnitude and duration of Δ^9-THC-induced impairment. Overall, our results confirm that Δ^9-THC impairs aspects of driving performance and demonstrate that the magnitude and duration of this impairment depends on the dose provided, route of administration and frequency with which cannabis is used. There appears to be no universal answer to the question of "*how long to wait before driving?*" following cannabis use: consideration of multiple factors is therefore required to determine appropriate delays between Δ^9-THC use and the performance of safety-sensitive tasks.

Several measures of driving performance (i.e. Lateral Control, SDLP

Table 8
Results of the inhaled and oral Δ^9-THC meta-regression analyses.

				Unexplained Heterogeneity		
Covariate	Effect Estimates (*n*)/ Mean; Median (IQR)	Hedges' *g* (95% CIs)	*p*-value	I^2-value	*p*-value	Sigma
Inhaled Δ^9-THC Model (Includes "Regular" and "Other" Users) (*n* = 579 effect estimates):						
Intercept	–	–0.2356 (–0.3753, –0.0959)	**0.001**			
Performance Domain	–	–	–			
[a]Conflict Control	48	–	–			
Divided Attention	106	–0.0767 (–0.1687, +0.0154)	0.102			
Fluid Intelligence	20	–0.0859 (–0.1945, +0.0228)	0.121			
Information Processing	82	–0.1318 (–0.2310, –0.0327)	**0.009**			
SDLP (Only)	20	–0.0686 (–0.2279, +0.0906)	0.398			
Reaction Time	29	$+4.7 \times 10^{-5}$ (–0.1209, +0.1210)	0.999			
Sustained Attention	37	+0.0696 (–0.0892, +0.2283)	0.390			$\sigma_1^2 = 0.001$
Tracking Performance	89	–0.0790 (–0.1659, +0.0079)	0.075	55.5	<0.001	$\sigma_2^2 = 0.001$
Working Memory	148	–0.0356 (–0.1261, +0.0548)	0.439			$\sigma_3^2 = 0.045$
Cannabis Use Behaviour	–	–	–			
[a]Other Users	483	–	–			
Regular Users	91	+0.1707 (+0.0572, +0.2843)	**0.003**			
Route of Administration	–	–	–			
[a]Smoking	296	–	–			
Vaporisation	278	–0.0898 (–0.1658, –0.0138)	**0.021**			
Dose of Δ^9-THC	23; 21 (10, 26)	–0.0048 (–0.0073, –0.0024)	**<0.001**			
Time Interval	155; 110 (45, 240)	+0.0005 (+0.0004, +0.0007)	**<0.001**			
Inhaled Δ^9-THC Model ("Regular" Users, Only) (*n* = 59 effect estimates):						
Intercept	–	–0.5614 (–0.9849, –0.1379)	0.101			
Performance Domain	–	–	–			
[a]Conflict Control	19	–	–			
Fluid Intelligence	13	–0.1017 (–0.2635, +0.0601)	0.213			
Sustained Attention	12	+0.0494 (–0.4163, +0.5150)	0.832			$\sigma_1^2 = 0.009$
Tracking Performance	15	+0.1443 (–0.0279, +0.3165)	0.099	36.5	0.061	$\sigma_2^2 = 0.011$
Route of Administration	–	–	–			$\sigma_3^2 < 0.001$
[a]Smoking	20	–	–			
Vaporisation	39	+0.2081 (–0.1142, +0.5305)	0.201			
Dose of Δ^9-THC	30; 21 (21, 26)	+0.0034 (–0.0057, +0.0124)	0.462			
Time Interval	72; 40 (40, 60)	+0.0004 (–0.0008, +0.0017)	0.508			
Inhaled Δ^9-THC Model ("Other" Users) (*n* = 481 effect estimates):						
Intercept	–	–0.0999 (–0.2553, +0.0555)	0.207			
Performance Domain	–	–	–			
[a]Conflict Control	29	–	–			
Divided Attention	97	–0.1877 (–0.3134, –0.0621)	**0.004**			
Information Processing	78	–0.2419 (–0.3704, –0.1135)	**<0.001**			
SDLP (Only)	16	–0.2112 (–0.3826, –0.0399)	**0.016**			
Reaction Time	22	–0.1080 (–0.2786, +0.0627)	0.214			$\sigma_1^2 < 0.001$
Sustained Attention	25	+0.0073 (–0.1679, +0.1824)	0.935	30.8	0.096	$\sigma_2^2 = 0.004$
Tracking Performance	74	–0.1894 (–0.3088, –0.0700)	**0.002**			$\sigma_3^2 = 0.013$
Working Memory	140	–0.1318 (–0.2541, –0.0094)	**0.035**			
Route of Administration	–	–	–			
[a]Smoking	256	–	–			
Vaporisation	225	–0.0233 (–0.1219, +0.0753)	0.642			
Dose of Δ^9-THC	22; 18 (10, 25)	–0.0082 (–0.0112, –0.0053)	**<0.001**			
Time Interval	171; 120 (60, 240)	+0.0005 (+0.0004, +0.0007)	**<0.001**			
Oral Δ^9-THC Model (*n* = 243 effect estimates):						
Intercept	–	–0.3345 (–0.5284, –0.1405)	**<0.001**			
Performance Domain	–	–	–			
[a]Conflict Control	11	–	–			
Divided Attention	42	+0.2833 (+0.0422, +0.5243)	**0.022**			
Fine Motor Function	32	+0.2314 (–0.0056, +0.4684)	0.056			
Information Processing	46	+0.1278 (–0.1114, +0.3670)	0.294			$\sigma_1^2 = 0.011$
Reaction Time	18	+0.1832 (–0.0187, +0.3852)	0.075	40.7	0.003	$\sigma_2^2 = 0.003$
Sustained Attention	11	+0.2960 (+0.0219, +0.5701)	**0.034**			$\sigma_3^2 = 0.015$
Tracking Performance	33	+0.1118 (–0.1299, +0.3535)	0.363			
Working Memory	50	+0.3092 (+0.0778, +0.5407)	**0.009**			
Dose of Δ^9-THC	21; 15 (10–25)	–0.0087 (–0.0129, –0.0046)	**<0.001**			
Time Interval	238; 180 (120–360)	–0.0002 (–0.0005, +0.0001)	0.267			
Time Interval (Curvilinear)	–	$+2.0 \times 10^{-6}$ ($+1.0 \times 10^{-6}$, $+3.0 \times 10^{-6}$)	**0.007**			

SDLP: Standard Deviation of Lane Position. *a*: Reference group in analyses of categorical variables. Analyses were performed as per Sect. 2.6.3b 'Meta-Regression Analysis'. Details of included studies are summarised in Table 5 and presented in Supplementary File 4. A description of each cognitive task can be found in Supplementary File 2. All effect estimates included in the analysis of oral Δ^9-THC model were derived from trials of "Other Users" (none of those derived from "Regular Users" were eligible for inclusion). The Post-Treatment Time Interval covariate was centred in the orally administered Δ^9-THC analysis; all values substituted into this equation should therefore be centred (i.e. by subtracting the mean value (see 'Effect estimates (*n*)/Mean; Median (IQR)').

Table 9
Summary of the Δ^9-THC's predicted effects of on car driving and related cognitive functions.

		Predicted 'Peak' Effect at 20 mg Δ^9-THC [a] (Other Cannabis Users, Only) (Hedges' *g*)			Predicted 'Recovery' Time at 20 mg Δ^9-THC [b] (Other Cannabis Users, Only) (min)		
Cognitive Domain	Δ^9-THC Effect [c]	Smoked	Vaporised	Oral [d]	Smoked	Vaporised	Oral
Cognitive Functions:							
Divided Attention	Negative	–0.45	–0.48	–0.23	383	428	- [e]
Tracking Performance	Negative	–0.45	–0.48	–0.40	386	430	573
Information Processing	Negative	–0.51	–0.53	–0.39	486	530	557
Conflict Control	Negative	–0.26	–0.29	–0.51	<60	71	665
Fluid Intelligence	Negative	–	–	–	–	–	–
Reaction Time	Negative	–0.37	–0.40	–0.33	232	276	492
Fine Motor Function	Negative	–	–	–0.28	–	–	415
Gross Motor Function	-	–	–	–	–	–	–
Sensory Discrimination	Unclear	–	–	–	–	–	–
Time Perception	Unclear	–	–	–	–	–	–
Sustained Attention	Negative	–0.26	–0.28	–0.22	<60	<60	- [e]
Working Memory	Negative	–0.40	–0.42	–0.20	277	321	- [e]
Car Driving:							
Lateral Control	Negative						
SDLP (Only)	Negative	–0.48	–0.50	–	427	472	–
Speed	Unclear	–	–	–	–	–	–
Speed Variability	Unclear	–	–	–	–	–	–
CF Headway	Unclear	–	–	–	–	–	–
CF Headway Variability	Unclear	–	–	–	–	–	–
Reaction Time	Negative	–	–	–	–	–	–
[a]Other	–	–	–	–	–	–	–
Aggregate Effect [f]	–	–0.40	–0.42	–0.32	300	350	480

'-': Could not be calculated; CF: Car Following; SDLP: Standard Deviation of Lane Position. All negative effect estimates indicate a detrimental effect of Δ^9-THC, irrespective of the performance outcome. *a*: Values predicted on the basis of the 'Inhaled Δ^9-THC Model ("Other" Users)' in Table 8; *b*: 'Recovery Time' taken as the length of time required for Δ^9-THC's effects to dissipate to a level at which they are unlikely to have a "meaningful" impact on performance – that is, Hedges' $g = -0.25$ (with values predicted on the basis of the 'Oral Δ^9-THC Model' in Table 8); *c*: Based on the results of the meta-analyses of 'peak' Δ^9-THC effects; *d*: 'Peak' effect predicted to occur 283 min post-Δ^9-THC treatment; *e*: The 'peak' effect at a Δ^9-THC dose of 20 mg is predicted to be less impairing than Hedges' $g = -0.25$.

[Only], Reaction Time) and driving-related cognitive skills (i.e. Fluid Intelligence, Divided Attention, Tracking Performance, Information Processing, Conflict Control, Reaction Time, Fine Motor Function, Sustained Attention, Woking Memory) exhibited significant impairment in the initial meta-analyses of "peak" Δ^9-THC effects. While significant changes were not identified for some other skills (i.e. CF Headway, CF Headway Variability, Speed, Speed Variability, Sensory Discrimination, Time Perception), these results should be interpreted with caution as relatively few studies were available in these domains. Additionally, although this review found no effect of Δ^9-THC on *accuracy* of Time Perception; that is, how far the estimated times were from the target times, other studies report significant effects on *absolute* Time Perception – indicating *change* in perception, but not *impairment* per se (Anderson et al., 2010b; McDonald et al., 2003; Sewell et al., 2013). Δ^9-THC could also affect time perception in both directions; that is, it could increase the likelihood of both over- and under-estimation on time estimation and time reproduction tests, thus, increasing the spread of the data set without altering the mean performance score. The initial meta-analyses also revealed a non-significant trend for a positive effect of Δ^9-THC on driving speed (i.e. *reduced* average speed), suggesting drivers may attempt to expand their "safety margins" when operating a vehicle under the influence of Δ^9-THC (likely due to reduced driving confidence (Arkell et al., 2019, 2020)).

The current study used multiple meta-regression analyses to generate mathematical models that could predict the magnitude and duration of Δ^9-THC-induced impairment. While the first model was found to be limited in its ability to simultaneously describe inhaled Δ^9-THC's effects in 'Regular' and 'Other' (mostly occasional) cannabis users, it did reveal significant differences between these populations. Specifically, Regular Cannabis Use (i.e. weekly or more often) was associated with less cognitive impairment following acute Δ^9-THC administration. A recent systematic review likewise concluded that cannabis has less pronounced behavioural and physiological effects in regular (than occasional) users (Colizzi and Bhattacharyya, 2018). Indeed, pharmacodynamic events such as downregulation of the cannabinoid type 1 receptor, receptor conformational change, and receptor internalisation have been proposed to explain the observed tolerance to Δ^9-THC's effects (Ramaekers et al., 2020).

It is, however, important to acknowledge the limitations of this analysis. First, the Other Cannabis Users are a heterogeneous population, as studies often included participants who used cannabis at different frequencies. Second, it should be acknowledged that studies of Regular Cannabis Users used a variety of methods to 'standardise' participants' pre-trial cannabis intakes. Specifically, some instructed participants to: (1) abstain for ≥24 h (Brands et al., 2019; Mason et al., 2019; Spronk et al., 2016); (2) abstain overnight or on the morning prior to testing (Ramaekers et al., 2016; Weinstein et al., 2008); (3) continue using cannabis as 'usual' (Ramaekers et al., 2009; Van Wel et al., 2013); or (4) did not specifically state their method (Matheson et al., 2020). Each of these approaches has the potential to elicit subtly different effects (e.g. due to residual Δ^9-THC in blood or the development of withdrawal symptoms (Budney et al., 2008)). Finally, it is important to recognise that although Regular Cannabis Users appear to be less impaired than Other Cannabis Users when administered a fixed dose of Δ^9-THC, some of these individuals (e.g. recreational cannabis users) might use larger doses of Δ^9-THC (i.e. because of their increased tolerance to its effects), resulting in an equivalent amount of impairment.

None of the covariates included in the subsequent meta-regression analysis of inhaled Δ^9-THC's effects in Regular Cannabis Users (*only*) were significantly related to effect size. This may reflect the fact that most outcomes were measured under similar experimental conditions; that is, between 20–60 min post-treatment (90 % of outcomes) and at a dose of 21–26 mg Δ^9-THC (71 % of outcomes).

In contrast, several covariates were significantly related to effect size in the analysis of inhaled Δ^9-THC's effects in Other Cannabis Users (*only*). Specifically, cognitive impairment increased with Δ^9-THC Dose and decreased over the Post-Treatment Time Interval; it also varied across the Performance Domains. The model therefore explained a relatively large proportion of the variance observed (pseudo-$R^2 = 0.64$) and was used to predict the magnitude and duration of Δ^9-THC-induced

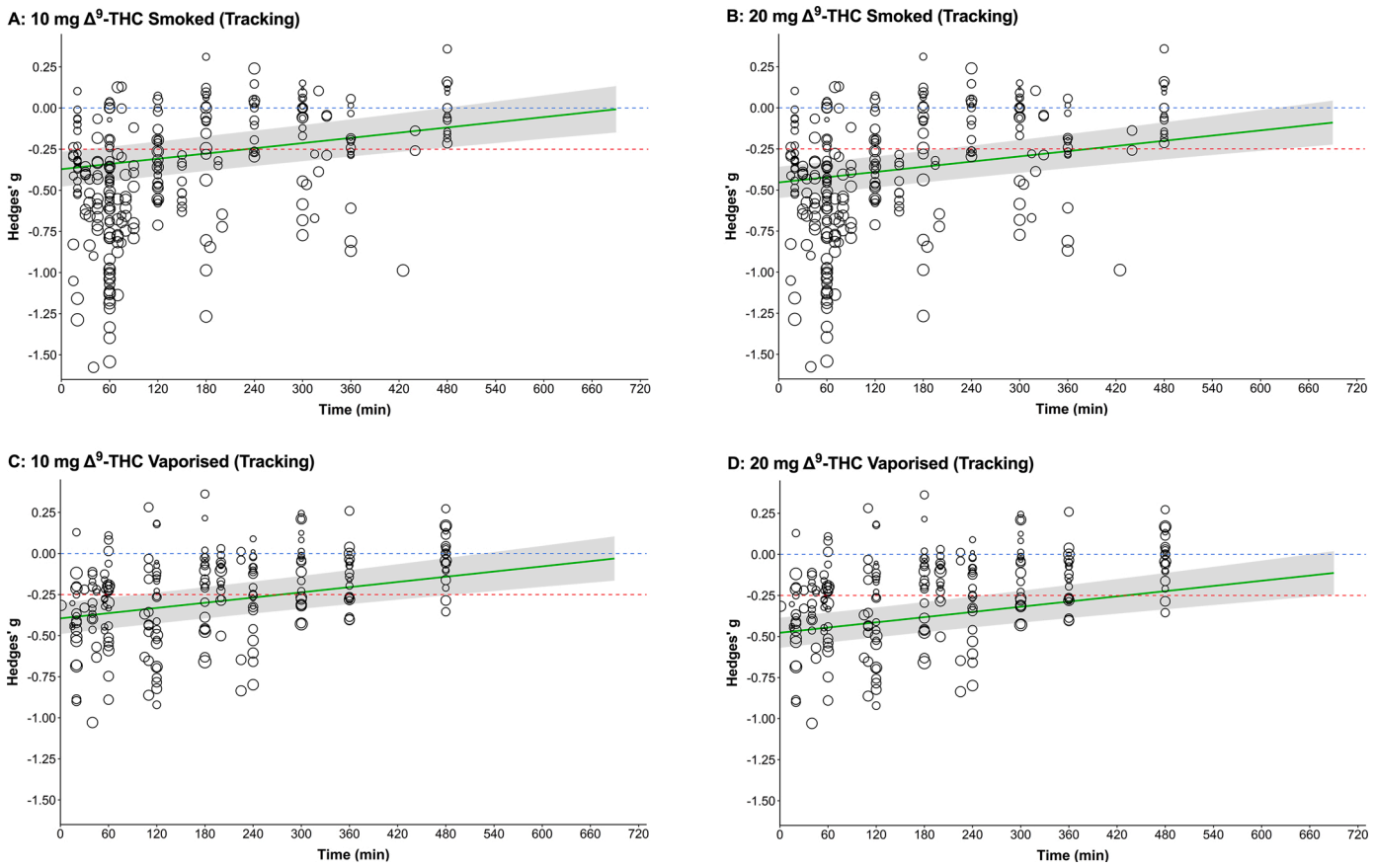


Fig. 2. The predicted relationship between the Post-Treatment Time Interval and the Hedges' *g* (95 % CI) effect of Δ^9-THC on tracking performance (as an example) when administered via (A) Smoking (10 mg); (B) Smoking (20 mg); (C) Vaporisation (10 mg); and (D) Vaporisation (20 mg) (based on models presented in Table 8). These predictions are based on 'Other Cannabis Users' (only). 'Smoked' outcomes only shown in Figures A and B and 'Vaporised' outcomes only shown in Figures C and D (although all outcomes contributed to both regression models). Red line represents a Hedges' g effect of –0.25 (likely recovered or minimal impairment detected) and the blue line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Actual (uncontrolled) effect estimates shown.

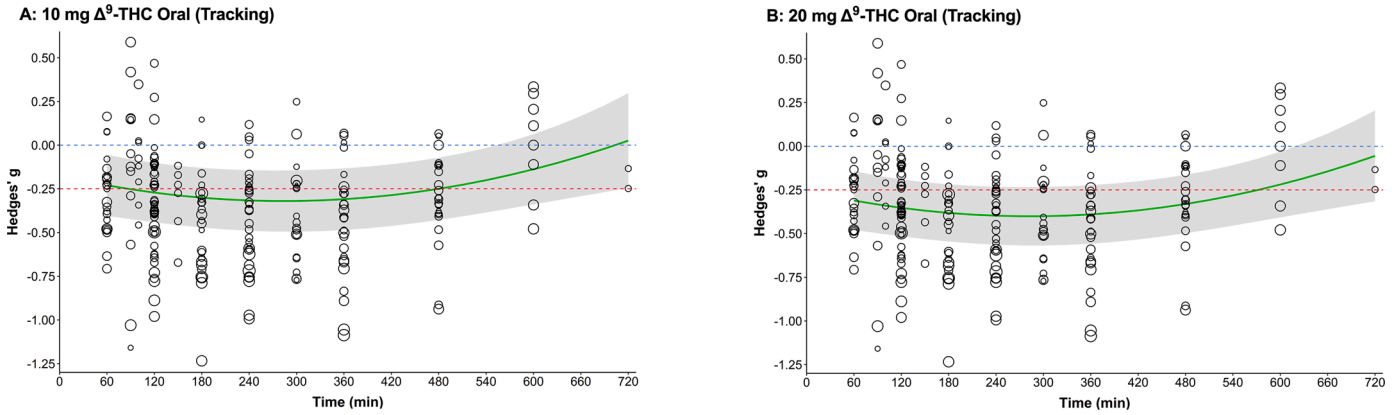


Fig. 3. The predicted relationship between the Post-Treatment Time Interval and the Hedges' *g* (95 % CI) effect of Δ^9-THC on tracking performance (as an example) when administered via (A) Oral (10 mg); and (B) Oral (20 mg) (based on models presented in Table 8). These predictions are based on 'Other Cannabis Users' (only). Red line represents a Hedges' g effect of –0.25 (likely recovered or minimal impairment detected) and the blue line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Actual (uncontrolled) effect estimates shown.

impairment (as illustrated in Table 9). Indeed, our analyses suggest that most driving-related cognitive skills recover (Hedges' *g*=–0.25) within ~3- and ~5-hs of inhaling 10 and 20 mg of Δ^9-THC, respectively (with almost all recovering within ~5- and ~7-hs, respectively).

The residual variance in both models could be due to a number of factors including: (1) the dose of Δ^9-THC being quantified as an *absolute*, rather than *relative*, amount (as too few studies reported participants' body weight to calculate relative doses); (2) the heterogenous cannabis use behaviour of the Other Cannabis Users and the different methods used to 'standardise' the pre-trial cannabis intakes of Regular Cannabis Users (as discussed above); (3) the fact that some studies administered Δ^9-THC in combination with placebo treatments (e.g. placebo alcohol),

tobacco and other cannabinoids and/or cannabis constituents; and (4) the variety of driving and neuropsychological tests employed with differing demands and sensitivities. Results should therefore be interpreted with some consideration that these potential moderators are not captured in the model. The extent to which different populations and contexts are represented in each model should also be considered. For example, these findings may be limited in their generalisability to females as they were underrepresented in the sample – particularly given that the dose was not relative and that Δ^9-THC has been reported to elicit different effects between sexes (Anderson et al., 2010a, b; Matheson et al., 2020).

Several covariates were also significantly related to effect size in the multiple meta-regression analysis of oral Δ^9-THC's effects. Specifically, cognitive impairment increased with Δ^9-THC Dose and differed across the Performance Domains and Post-Treatment Time Interval. That is, oral Δ^9-THC-induced impairment indicated a curvilinear (U-shaped) relationship with time (broadly comparable to that of its pharmacokinetic profile (Vandrey et al., 2017)). While this model was considered adequate to estimate the magnitude and duration of oral Δ^9-THC's cognitive effects (see Table 9), the larger amount of unexplained variance (pseudo-$R^2 = 0.28$) (i.e. compared to the model of inhaled Δ^9-THC) suggests that results should be interpreted with greater caution. This additional variability may be a consequence of oral Δ^9-THC's complex pharmacokinetic profile. In particular, the fact that time to reach peak blood Δ^9-THC and 11-OH-Δ^9-THC concentrations (T_{max}) tends to differ as a function of dose (i.e. higher oral doses may have longer T_{max} values than lower oral doses) (Vandrey et al., 2017); which is not typically the case for inhaled Δ^9-THC (Spindle et al., 2019) and could not be captured in this meta-regression model. Oral Δ^9-THC absorption can also be erratic, leading to an inconsistent pharmacokinetic response (Ohlsson et al., 1980). Nonetheless, this model offers some insight to the time course of oral Δ^9-THC-induced cognitive impairment (as illustrated in Table 9) suggesting that impairment of most driving-related cognitive skills takes ~8-hs to subside (Hedges' g=–0.25) after oral consumption of 20 mg of Δ^9-THC.

The results of the current review suggest that some measures of driving performance and driving-related cognitive skills may be more sensitive to the impairing effects of Δ^9-THC than others. It is also interesting to note that SDLP (Only) was one of the outcomes that demonstrated the greatest sensitivity to Δ^9-THC's effects (although it could only be investigated in the model of inhaled Δ^9-THC's effects in Other Cannabis Users). This finding highlights the importance of simulated and on-road driving studies in this area of research.

This review identified a small number of studies investigating the acute effects of Δ^9-THC on driving-related cognitive skills in clinical populations (e.g. psychotic disorders, diabetic neuropathy, Tourette syndrome, attention deficit hyperactivity disorder [ADHD], dementia). The medical conditions studied were too heterogenous to consolidate into a meaningful meta-analysis. Nonetheless, results were relatively consistent with Δ^9-THC indicating either a small negative or positive Hedges' g effect on the majority (87 %) of outcomes examined. These subtle (in most instances, non-significant) effects could partly reflect the low doses of Δ^9-THC (e.g. $\leq$ 5.0 mg orally) administered in some studies. However, these doses were still sufficient to elicit some therapeutic effects (e.g. decreased hyperactivity and impulsivity in ADHD, decreased neuropathic pain) (Cooper et al., 2017; Wallace et al., 2015). Alternatively, it is possible that Δ^9-THC ameliorated clinical symptoms that were previously impairing cognitive and psychomotor performance, thereby offsetting its detrimental effects. Further research investigating the impact of therapeutically-relevant Δ^9-THC doses on measures of driving performance and associated cognitive skills in clinical populations is therefore warranted. Importantly, the results of the above meta-regression analyses suggest that a chronic dosing phase (allowing for adaptation to Δ^9-THC's effects) should also be utilised in such studies with patients. The fact that medical cannabis users are almost invariably regular users seeking to reverse troubling clinical symptoms limits the applicability of the findings of the current review to this specific population.

This review has several other limitations. First, only English language articles were included. Second, of the 1456 outcomes (derived from studies of healthy participants) in this review, 31 % (445) were ineligible for quantitative synthesis because an effect estimate could not be calculated, or the outcome was derived from a study that scored <50 % on the Rosendal scale; additional outcomes and studies were also excluded because results were not adequately reported (Supplementary Files 1 & 2). Third, the meta-regression models developed assume a fixed rate of recovery at a given dose of Δ^9-THC, route of administration and performance domain. Fourth, as trials often measured cognitive performance multiple times and/or on multiple tasks generating multiple outcomes, these contributed different amounts of data to the review; the current analyses are therefore biased toward studies that contributed more effect estimates. However, given the aim of this review, it would not have been appropriate to average effect estimates across multiple measures (Scammacca et al., 2014)). Fifth, the few studies that measured driving performance or a driving-related cognitive skill >12 h following acute Δ^9-THC administration were excluded to minimise the influence of their unique confounding factors (e.g. sleep, access to cannabis between assessments). Finally, a limitation of the research area as a whole is the small number of studies involving regular cannabis users and longer post-treatment time intervals (e.g. 4–6 h).

This systematic review used evidence from recent studies investigating the acute effects of Δ^9-THC on car driving performance and discrete cognitive skills related to car driving to generate meta-regression models that predict the magnitude and duration of Δ^9-THC-induced impairment. Findings suggest individuals should wait at least 5-hs following inhaled cannabis use before performing safety-sensitive tasks, although the recovery time required will depend on several factors (in particular, Δ^9-THC dose); oral Δ^9-THC-induced impairment may also take longer to subside. Further research involving regular cannabis users and longer post-treatment time intervals would permit better characterisation of Δ^9-THC's effects and help inform the development of guidelines and drug-driving legislation to promote safe driving practices following Δ^9-THC and cannabis use.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Danielle McCartney, Thomas R. Arkell and Iain S. McGregor receive salary support from the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for medicinal cannabis research at the University of Sydney.

Declaration of Competing Interest

None.

Acknowledgements

The authors would first like to thank those researchers who generously donated raw performance data for this investigation; Eliza Pabon, Harriet de Wit, Michael Ballard, Nicolas Schlienz, Tory Spindle, Ryan Vandrey, Edward Cone, Evan Herrmann, George Bigelow, John Mitchell, Ronald Flegel, Charles LoDico, Elia Goffi, Elise Weerts, Ruth Winecker and Eugene Hayes. They would also like to thank Dr Matt Stainer of Griffith University (Queensland, Australia) for his assistance in generating meta-regression graphs. We are grateful to Barry and Joy Lambert and family for their ongoing support of the research activities of the Lambert Initiative for Cannabinoid Therapeutics.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.01.003.

References

Anderson, B.M., Rizzo, M., Block, R.I., Pearlson, G.D., O'Leary, D.S., 2010a. Sex differences in the effects of marijuana on simulated driving performance. J. Psychoac. Drugs 42, 19–30.

Anderson, B.M., Rizzo, M., Block, R.I., Pearlson, G.D., O'Leary, D.S., 2010b. Sex, drugs, and cognition: effects of marijuana. J. Psychoac. Drugs 42, 413–424.

Arkell, T.R., Lintzeris, N., Kevin, R.C., Ramaekers, J.G., Vandrey, R., Irwin, C., Haber, P. S., McGregor, I.S., 2019. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology 236, 2713–2724.

Arkell, T.R., Vinckenbosch, F., Kevin, R., Theunissen, E.F., McGregor, I.S., Ramaekers, J. G., 2020. Effect of cannabidiol and delta-9-tetrahydrocannabinol on driving performance: a randomized clinical trial. JAMA.

Arkell, T.R., Lintzeris, N., Mills, L., Suraev, A., Bravo, M., Arnold, J.C., McGregor, I.S., 2020a. Driving-related behaviours, attitudes and perceptions among australian medical Cannabis users: results from the CAMS 18-19 survey. Accid. Anal. Prev.

Arkell, T.R., Spindle, T.R., Kevin, R., Vandrey, R., McGregor, I.S., 2020b. Using per se limits to define cannabis-induced driving impairment: problems, pitfalls and possible solutions. Traffic Inj. Prev.

Assink, M., Wibbelink, C.J., 2016. Fitting three-level meta-analytic models in R: a step-by-step tutorial. Quant. Methods Psychol. 12, 154–174.

Ballard, M.E., de Wit, H., 2011. Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers. Pharmacol. Biochem. Behav. 97, 627–631.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Malhi, S., Giampietro, V., Williams, S., Brammer, M., Rubia, K., Collier, D.A., McGuire, P.K., 2015. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. Eur. Neuropsychopharmacol. 25, 26–37.

Bonar, E.E., Cranford, J.A., Arterberry, B.J., Walton, M.A., Bohnert, K.M., Ilgen, M.A., 2019. Driving under the influence of cannabis among medical cannabis patients with chronic pain. Drug Alcohol Depend. 195, 193–197.

Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2011. Introduction to Meta-analysis. John Wiley & Sons.

Bosker, W.M., Kuypers, K.P.C., Theunissen, E.L., Surinx, A., Blankespoor, R.J., Skopp, G., Jeffery, W.K., Walls, H.C., van Leeuwen, C.J., Ramaekers, J.G., 2012. Medicinal Δ 9-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. Addiction 107, 1837–1844.

Brands, B., Mann, R.E., Wickens, C.M., Sproule, B., Stoduto, G., Sayer, G.S., Burston, J., Pan, J.F., Matheson, J., Stefan, C., George, T.P., Huestis, M.A., Rehm, J., Le Foll, B., 2019. Acute and residual effects of smoked cannabis: impact on driving speed and lateral control, heart rate, and self-reported drug effects. Drug Alcohol Depend. 205.

Brown, T., McConnell, M., Rupp, G., Meghdadi, A., Richard, C., Schmitt, R., Gaffney, G., Milavetz, G., Berka, C., 2019. Correlation of EEG biomarkers of cannabis with measured driving impairment. Traffic Inj. Prev. 20, S148–S151.

Broyd, S.J., van Hell, H.H., Beale, C., Yuecel, M., Solowij, N., 2016. Acute and chronic effects of cannabinoids on human cognition—a systematic review. Biol. Psychiatry 79, 557–567.

Budney, A.J., Vandrey, R.G., Hughes, J.R., Thostenson, J.D., Bursac, Z., 2008. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. J. Subst. Abuse Treat. 35, 362–368.

MADD Canada, 2019. Cannabis and Driving.

Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., 2019. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Routledge.

Colizzi, M., Bhattacharyya, S., 2018. Cannabis use and the development of tolerance: a systematic review of human evidence. Neurosci. Biobehav. Rev. 93, 1–25.

Cooper, R.E., Williams, E., Seegobin, S., Tye, C., Kuntsi, J., Asherson, P., 2017. Cannabinoids in attention-deficit/hyperactivity disorder: a randomised-controlled trial. Eur. Neuropsychopharmacol. 27, 795–808.

Dassanayake, T., Michie, P., Carter, G., Jones, A., 2011. Effects of benzodiazepines, antidepressants and opioids on driving. Drug Saf. 34, 125–156.

DiGuiseppi, C.G., Smith, A.A., Betz, M.E., Hill, L., Lum, H.D., Andrews, H., Leu, C.-S., Hyde, H.A., Eby, D.W., Li, G., 2019. Cannabis use in older drivers in Colorado: the LongROAD Study. Accid. Anal. Prev. 132, 105273.

Ginsburg, B.C., 2019. Strengths and limitations of two cannabis-impaired driving detection methods: a review of the literature. Am. J. Drug Alcohol Abuse 45, 610–622.

Hartman, R.L., Huestis, M.A., 2013. Cannabis effects on driving skills. Clin. Chem. 59, 478–492.

Hartman, R.L., Brown, T.L., Milavetz, G., Spurgin, A., Pierce, R.S., Gorelick, D.A., Gaffney, G., Huestis, M.A., 2015. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend. 154, 25–37.

Health Canada, 2019. Lower Risk Cannabis Use Guidelines.

Irwin, C., Iudakhina, E., Desbrow, B., McCartney, D., 2017. Effects of acute alcohol consumption on measures of simulated driving: a systematic review and meta-analysis. Accid. Anal. Prev. 102, 248–266.

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J.M., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control. Clin. Trials 17, 1–12.

Li, M.-C., Brady, J.E., DiMaggio, C.J., Lusardi, A.R., Tzong, K.Y., Li, G., 2012. Marijuana use and motor vehicle crashes. Epidemiol. Rev. 34, 65–72.

Macdonald, S., 2019. Cannabis Crashes: Myths & Truths. Lulu. com.

Madras, B.K., 2017. Are THC Levels in Oral Fluids and Blood Plasma Comparable after Oral Ingestion of Edibles Containing Cannabis or THC? Clin. Chem. 63, 629–631.

Maher, C.G., Moseley, A.M., Sherrington, C., Elkins, M.R., Herbert, R.D., 2008. A description of the trials, reviews, and practice guidelines indexed in the PEDro database. Phys. Ther. 88, 1068–1077.

Mason, N.L., Theunissen, E.L., Hutten, N.R.P.W., Tse, D.H.Y., Toennes, S.W., Jansen, J.F. A., Stiers, P., Ramaekers, J.G., 2019. Reduced responsiveness of the reward system is associated with tolerance to cannabis impairment in chronic users. Addict. Biol.

Matheson, J., Sproule, B., Di Ciano, P., Fares, A., Le Foll, B., Mann, R.E., Brands, B., 2020. Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. Psychopharmacology 237, 305–316.

McDonald, J., Schleifer, L., Richards, J.B., De Wit, H., 2003. Effects of THC on behavioral measures of impulsivity in humans. Neuropsychopharmacology 28, 1356–1365.

Micallef, J., Dupouey, J., Jouve, E., Truillet, R., Lacarelle, B., Taillard, J., Daurat, A., Authie, C., Blin, O., Rascol, O., Philip, P., Mestre, D., 2018. Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. Fundam. Clin. Pharmacol. 32, 558–570.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 1.

Morrison, P.D., Zois, V., McKeown, D.A., Lee, T.D., Holt, D.W., Powell, J.F., Kapur, S., Murray, R.M., 2009. The acute effects of synthetic intravenous 9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol. Med. 39, 1607–1616.

Moskowitz, H., Fiorentino, D., 2000. In: ADMINISTRATION, U.S.D.O.T.N.H.T.S (Ed.), A Review of the Literature on the Effects of Low Doses of Alcohol on Driving-Related Skills. Washington, D.C.

Nakagawa, S., Schielzeth, H., 2013. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol. Evol. 4, 133–142.

National Academies of Sciences Engineering and Medicine, 2017. The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research. Washington, DC.

Ohlsson, A., Lindgren, J., Wahlen, A., Agurell, S., Hollister, L., Gillespie, H., 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin. Pharmacol. Ther. 28, 409–416.

Oomen, P.P., van Hell, H.H., Bossong, M.G., 2018. The acute effects of cannabis on human executive function. Behav. Pharmacol. 29, 605–616.

Pabon, E., de Wit, H., 2019. Developing a phone-based measure of impairment after acute oral Δ9-tetrahydrocannabinol. J. Psychopharmacol. 33, 1160–1169.

Ramaekers, J.G., 2018. Driving under the influence of cannabis: an increasing public health concern. Jama 319, 1433–1434.

Ramaekers, J.G., Robbe, H.W.J., O'Hanlon, J.F., 2000. Marijuana, alcohol and actual driving performance. Hum. Psychopharmacol. Clin. Exp. 15, 551–558.

Ramaekers, J.G., Kauert, G., Theunissen, E.L., Toennes, S.W., Moeller, M.R., 2009. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. J. Psychopharmacol. 23, 266–277.

Ramaekers, J.G., van Wel, J.H., Spronk, D.B., Toennes, S.W., Kuypers, K.P.C., Theunissen, E.L., Verkes, R.J., 2016. Cannabis and tolerance: acute drug impairment as a function of cannabis use history. Sci. Rep. 6.

Ramaekers, J.G., Mason, N.L., Theunissen, E.L., 2020. Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. Eur. Neuropsychopharmacol. 36, 191–205.

Rogeberg, O., 2019. A meta-analysis of the crash risk of cannabis-positive drivers in culpability studies—avoiding interpretational bias. Accid. Anal. Prev. 123, 69–78.

Rogeberg, O., Elvik, R., 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction 111, 1348–1359.

Rogeberg, O., Elvik, R., 2017. Response to Li et al.(2017): cannabis use and crash risk in drivers. Addiction 112, 1316-1316.

Ronen, A., Gershon, P., Drobiner, H., Rabinovich, A., Bar-Hamburger, R., Mechoulam, R., Cassuto, Y., Shinar, D., 2008. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. Accid. Anal. Prev. 40, 926–934.

Ronen, A., Chassidim, H.S., Gershon, P., Parmet, Y., Rabinovich, A., Bar-Hamburger, R., Cassuto, Y., Shinar, D., 2010. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accid. Anal. Prev. 42, 1855–1865.

Rotermann, M., 2020. What has changed since cannabis was legalized? Health Rep. 31, 11–20.

Scammacca, N., Roberts, G., Stuebing, K.K., 2014. Meta-analysis with complex research designs: dealing with dependence from multiple measures and multiple group comparisons. Rev. Educ. Res. 84, 328–364.

Schlienz, N.J., Spindle, T.R., Cone, E.J., Herrmann, E.S., Bigelow, G.E., Mitchell, J.M., Flegel, R., LoDico, C., Vandrey, R., 2020. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug Alcohol Depend., 107969

Sewell, R.A., Schnakenberg, A., Elander, J., Radhakrishnan, R., Williams, A., Skosnik, P. D., Pittman, B., Ranganathan, M., D'Souza, D.C., 2013. Acute effects of THC on time perception in frequent and infrequent cannabis users. Psychopharmacology 226, 401–413.

Spindle, T.R., Cone, E.J., Schlienz, N.J., Mitchell, J.M., Bigelow, G.E., Flegel, R., Hayes, E., Vandrey, R., 2018. Acute effects of smoked and vaporized Cannabis in healthy adults who infrequently use Cannabis a crossover trial. Jama Network Open 1.

Spindle, T.R., Cone, E.J., Schlienz, N.J., Mitchell, J.M., Bigelow, G.E., Flegel, R., Hayes, E., Vandrey, R., 2019. Acute pharmacokinetic profile of smoked and vaporized cannabis in human blood and oral fluid. J. Anal. Toxicol. 43, 233–258.

Spindle, T.R., Cone, E.J., Goffi, E., Weerts, E.M., Mitchell, J.M., Winecker, R.E., Bigelow, G.E., Flegel, R.R., Vandrey, R., 2020. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug Alcohol Depend., 107937

Spronk, D.B., Van der Schaaf, M.E., Cools, R., De Bruijn, E.R.A., Franke, B., van Wel, J.H. P., Ramaekers, J.G., Verkes, R.J., 2016. Acute effects of cocaine and cannabis on reversal learning as a function of COMT and DRD2 genotype. Psychopharmacology 233, 199–211.

van den Elsen, G.A.H., Tobben, L., Ahmed, A.I.A., Verkes, R.J., Kramers, C., Marijnissen, R.M., Rikkert, M., van der Marck, M.A., 2017. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: a randomised controlled crossover trial. J. Psychopharmacol. 31, 184–191.

Van Rosendal, S.P., Osborne, M.A., Fassett, R.G., Coombes, J.S., 2010. Guidelines for glycerol use in hyperhydration and rehydration associated with exercise. Sport. Med. 40, 113–139.

Van Wel, J.H.P., Kuypers, K.P.C., Theunissen, E.L., Toennes, S.W., Spronk, D.B., Verkes, R.J., Ramaekers, J.G., 2013. Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. Br. J. Pharmacol. 170, 1410–1420.

Vandrey, R., Herrmann, E.S., Mitchell, J.M., Bigelow, G.E., Flegel, R., LoDico, C., Cone, E.J., 2017. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. J. Anal. Toxicol. 41, 83–99.

Veldstra, J.L., Bosker, W.M., de Waard, D., Ramaekers, J.G., Brookhuis, K.A., 2015. Comparing treatment effects of oral THC on simulated and on-the-road driving performance: testing the validity of driving simulator drug research. Psychopharmacology 232, 2911–2919.

Verhagen, A.P., de Vet, H.C., de Bie, R.A., Kessels, A.G., Boers, M., Bouter, L.M., Knipschild, P.G., 1998. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J. Clin. Epidemiol. 51, 1235–1241.

Verster, J.C., Roth, T., 2011. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). Int. J. Gen. Med. 4, 359.

Wallace, M.S., Marcotte, T.D., Umlauf, A., Gouaux, B., Atkinson, J.H., 2015. Efficacy of inhaled Cannabis on painful diabetic neuropathy. J. Pain 16, 616–627.

Weinstein, A., Brickner, O., Lerman, H., Greemland, M., Bloch, M., Lester, H., Chisin, R., Sarne, Y., Mechoulam, R., Bar-Hamburger, R., Freedman, N., Even-Sapir, E., 2008. A study investigating the acute dose-response effects of 13 mg and 17 mg Δ 9-tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. J. Psychopharmacol. 22, 441–451.

Wong, K., Brady, J.E., Li, G., 2014. Establishing legal limits for driving under the influence of marijuana. Inj. Epidemiol. 1, 26.

Reviewed Papers

Ahmed, A.I., van den Elsen, G.A., Colbers, A., Kramers, C., Burger, D. M., van der Marck, M.A., Rikkert, M.G.O., 2015. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. Psychopharmacology 232, 2587-2595.

Ahmed, A.I.A., van den Elsen, G.A.H., Colbers, A., van der Marck, M. A., Burger, D.M., Feuth, T.B., Rikkert, M.G.M.O., Kramers, C., 2014. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial. European Neuropsychopharmacology 24, 1475-1482.

Anderson, B.M., Rizzo, M., Block, R.I., Pearlson, G.D., O'Leary, D.S., 2010a. Sex Differences in the Effects of Marijuana on Simulated Driving Performance. Journal of Psychoactive Drugs 42, 19-30.

Anderson, B.M., Rizzo, M., Block, R.I., Pearlson, G.D., O'Leary, D.S., 2010b. Sex, Drugs, and Cognition: Effects of Marijuana. Journal of Psychoactive Drugs 42, 413-424.

Arkell, T.R., Lintzeris, N., Kevin, R.C., Ramaekers, J.G., Vandrey, R., Irwin, C., Haber, P.S., McGregor, I.S., 2019. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology 236, 2713-2724.

Atakan, Z., Bhattacharyya, S., Allen, P., Martin-Santos, R., Crippa, J., Borgwardt, S., Fusar-Poli, P., Seal, M., Sallis, H., Stahl, D., 2013. Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Δ 9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers. Psychological medicine 43, 1255-1267.

Ballard, M.E., de Wit, H., 2011. Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers. Pharmacology Biochemistry and Behavior 97, 627-631.

Battistella, G., Fornari, E., Thomas, A., Mall, J.F., Chtioui, H., Appenzeller, M., Annoni, J.M., Favrat, B., Maeder, P., Giroud, C., 2013. Weed or Wheel! fMRI, Behavioural, and Toxicological Investigations of How Cannabis Smoking Affects Skills Necessary for Driving. Plos One 8.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Malhi, S., Giampietro, V., Williams, S., Brammer, M., Rubia, K., Collier, D.A., McGuire, P.K., 2015. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. European Neuropsychopharmacology 25, 26-37.

Bhattacharyya, S., Crippa, J.A., Allen, P., Martin-Santos, R., Borgwardt, S., Fusar-Poli, P., Rubia, K., Kambeitz, J., O'Carroll, C., Seal, M.L., Giampietro, V., Brammer, M., Zuardi, A.W., Atakan, Z., McGuire, P.K., 2012. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Archives of General Psychiatry 69, 27-36.

Böcker, K.B.E., Gerritsen, J., Hunault, C.C., Kruidenier, M., Mensinga, T., Kenemans, J.L., 2010a. Cannabis with high Δ9-THC contents affects perception and visual selective attention acutely: An event-related potential study. Pharmacology Biochemistry and Behavior 96, 67-74.

Böcker, K.B.E., Hunault, C.C., Gerritsen, J., Kruidenier, M., Mensinga, T.T., Kenemans, J.L., 2010b. Cannabinoid Modulations of Resting State EEG Theta Power and Working Memory Are Correlated in Humans. Journal of Cognitive Neuroscience 22, 1906-1916.

Boggs, D.L., Cortes-Briones, J.A., Surti, T., Luddy, C., Ranganathan, M., Cahill, J.D., Sewell, A.R., D'Souza, D.C., Skosnik, P.D., 2018. The dose-dependent psychomotor effects of intravenous delta-9-tetrahydrocannabinol (Δ9-THC) in humans. Journal of Psychopharmacology 32, 1308-1318.

Borgwardt, S.J., Allen, P., Bhattacharyya, S., Fusar-Poli, P., Crippa, J. A., Seal, M.L., Fraccaro, V., Atakan, Z., Martin-Santos, R., O'Carroll, C., Rubia, K., McGuire, P.K., 2008. Neural Basis of Delta-9-Tetrahydrocannabinol and Cannabidiol: Effects During Response Inhibition. Biological Psychiatry 64, 966-973.

Bosker, W.M., Kuypers, K.P.C., Theunissen, E.L., Surinx, A., Blankespoor, R.J., Skopp, G., Jeffery, W.K., Walls, H.C., van Leeuwen, C.J., Ramaekers, J.G., 2012. Medicinal Δ 9-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. Addiction 107, 1837-1844.

Brands, B., Mann, R.E., Wickens, C.M., Sproule, B., Stoduto, G., Sayer, G.S., Burston, J., Pan, J.F., Matheson, J., Stefan, C., George, T.P., Huestis, M.A., Rehm, J., Le Foll, B., 2019. Acute and residual effects of smoked cannabis: Impact on driving speed and lateral control, heart rate, and self-reported drug effects. Drug and Alcohol Dependence 205.

Brown, T., McConnell, M., Rupp, G., Meghdadi, A., Richard, C., Schmitt, R., Gaffney, G., Milavetz, G., Berka, C., 2019. Correlation of EEG biomarkers of cannabis with measured driving impairment. Traffic Injury Prevention 20, S148-S151.

Colizzi, M., McGuire, P., Giampietro, V., Williams, S., Brammer, M., Bhattacharyya, S., 2018a. Modulation of acute effects of delta-9-tetrahydrocannabinol on psychotomimetic effects, cognition and brain function by previous cannabis exposure. European Neuropsychopharmacology 28, 850-862.

Colizzi, M., McGuire, P., Giampietro, V., Williams, S., Brammer, M., Bhattacharyya, S., 2018b. Previous Cannabis Exposure Modulates the Acute Effects of Delta-9-Tetrahydrocannabinol on Attentional Salience and Fear Processing. Experimental and Clinical Psychopharmacology 26, 582-598.

Cooper, R.E., Williams, E., Seegobin, S., Tye, C., Kuntsi, J., Asherson,

P., 2017. Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. European Neuropsychopharmacology 27, 795-808.

Curran, V.H., Brignell, C., Fletcher, S., Middleton, P., Henry, J., 2002. Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology 164, 61-70.

D'Souza, D., Pittman, B., Perry, E., Simen, A., 2009. Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans. Psychopharmacology 202, 569-578.

D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T.B., Krystal, J.H., 2005. Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. Biological Psychiatry 57, 594-608.

D'Souza, D.C., Braley, G., Blaise, R., Vendetti, M., Oliver, S., Pittman, B., Ranganathan, M., Bhakta, S., Zimolo, Z., Cooper, T., Perry, E., 2008a. Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Delta-9-tetrahydrocannabinol in humans. Psychopharmacology 198, 587-603.

D'Souza, D.C., Fridberg, D.J., Skosnik, P.D., Williams, A., Roach, B., Singh, N., Carbuto, M., Elander, J., Schnakenberg, A., Pittman, B., Sewell, R.A., Ranganathan, M., Mathalon, D., 2012. Dose-related modulation of event-related potentials to novel and target stimuli by intravenous δ 9-THC in humans. Neuropsychopharmacology 37, 1632-1646.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. Neuropsychopharmacology 29, 1558-1572.

D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E., Krystal, J., 2008b. Blunted psychotomimetic and amnestic effects of Δ-9- tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology 33, 2505-2516.

Dumont, G.J.H., van Hasselt, J.G.C., de Kam, M., van Gerven, J.M.A., Touw, D.J., Buitelaar, J.K., Verkes, R.J., 2011. Acute psychomotor, memory and subjective effects of MDMA and THC co-administration over time in healthy volunteers. Journal of Psychopharmacology 25, 478-489.

Gilman, J.M., Yucel, M.A., Pachas, G.N., Potter, K., Levar, N., Broos, H., Manghis, E.M., Schuster, R.M., Evins, A.E., 2019. Delta-9-tetrahydrocannabinol intoxication is associated with increased prefrontal activation as assessed with functional near-infrared spectroscopy: A report of a potential biomarker of intoxication. Neuroimage 197, 575-585.

Gray, K.M., Hart, C.L., Christie, D.K., Upadhyaya, H.P., 2008. Tolerability and effects of oral Δ9-tetrahydrocannabinol in older adolescents with marijuana use disorders. Pharmacology Biochemistry and Behavior 91, 67-70.

Haney, M., Malcolm, R.J., Babalonis, S., Nuzzo, P.A., Cooper, Z.D., Bedi, G., Gray, K.M., McRae-Clarke, A., Lofwall, M.R., Sparenborg, S., Walsh, S.L., 2016. Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. Neuropsychopharmacology 41, 1974-1982.

Hartman, R.L., Brown, T.L., Milavetz, G., Spurgin, A., Pierce, R.S., Gorelick, D.A., Gaffney, G., Huestis, M.A., 2015. Cannabis effects on driving lateral control with and without alcohol. Drug and Alcohol Dependence 154, 25-37.

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fañanás, L., Drukker, M., Ramaekers, J.G., Van Os, J., 2006. An experimental study of catechol-O-methyltransferase Val158Met moderation of Δ-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacology 31, 2748-2757.

Hindocha, C., Freeman, T.P., Xia, J.X., Shaban, N.D.C., Curran, H.V., 2017. Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial. Psychological Medicine 47, 2708-2719.

Hunault, C.C., Mensinga, T.T., Bocker, K.B.E., Schipper, C.M.A., Kruidenier, M., Leenders, M.E.C., de Vries, I., Meulenbelt, J., 2009. Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). Psychopharmacology 204, 85-94.

Hutten, N.R., Kuypers, K.P., van Wel, J.H., Theunissen, E.L., Toennes, S.W., Verkes, R.-J., Ramaekers, J.G., 2018. A single dose of cocaine enhances prospective memory performance. Journal of Psychopharmacology 32, 883-892.

Kollins, S.H., Schoenfelder, E.N., English, J.S., Holdaway, A., Van Voorhees, E., O'Brien, B.R., Dew, R., Chrisman, A.K., 2015. An exploratory study of the combined effects of orally administered methylphenidate and delta-9-tetrahydrocannabinol (THC) on cardiovascular function, subjective effects, and performance in healthy adults. Journal of Substance Abuse Treatment 48, 96-103.

Kowal, M.A., van Steenbergen, H., Colzato, L.S., Hazekamp, A., van der Wee, N.J.A., Manai, M., Durieux, J., Hommel, B., 2015. Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users. European Neuropsychopharmacology 25, 1943-1953.

Lamers, C.T.J., Ramaekers, J.G., 2001. Visual search and urban city driving under the influence of marijuana and alcohol. Human Psychopharmacology-Clinical and Experimental 16, 393-401.

Makela, P., Wakeley, J., Gijsman, H., Robson, P.J., Bhagwagar, Z., Rogers, R.D., 2006. Low doses of Δ-9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in young, healthy adults. Neuropsychopharmacology 31, 462-470.

Mason, N.L., Theunissen, E.L., Hutten, N., Tse, D.H.Y., Toennes, S. W., Stiers, P., Ramaekers, J.G., 2019a. Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity. European Neuropsychopharmacology 29, 247-256.

Mason, N.L., Theunissen, E.L., Hutten, N.R.P.W., Tse, D.H.Y., Toennes, S.W., Jansen, J.F.A., Stiers, P., Ramaekers, J.G., 2019b. Reduced responsiveness of the reward system is associated with tolerance to cannabis impairment in chronic users. Addiction Biology.

Matheson, J., Sproule, B., Di Ciano, P., Fares, A., Le Foll, B., Mann, R. E., Brands, B., 2020. Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. Psychopharmacology 237, 305-316.

McDonald, J., Schleifer, L., Richards, J.B., De Wit, H., 2003. Effects of THC on behavioral measures of impulsivity in humans. Neuropsychopharmacology 28, 1356-1365.

Menetrey, A., Augsburger, M., Favrat, B., Pin, M.A., Rothuizen, L.E., Appenzeller, M., Buclin, T., Mangin, P., Giroud, C., 2005. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg Dronabinol or of a cannabis decoction made with 20 or 60 mg Delta (9)-THC. Journal of Analytical Toxicology 29, 327-338.

Micallef, J., Dupouey, J., Jouve, E., Truillet, R., Lacarelle, B., Taillard, J., Daurat, A., Authie, C., Blin, O., Rascol, O., Philip, P., Mestre, D., 2018. Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. Fundamental & Clinical Pharmacology 32, 558-570.

Mokrysz, C., Freeman, T.P., Korkki, S., Griffiths, K., Curran, H.V., 2016. Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. Translational Psychiatry 6.

Morgan, C.J.A., Freeman, T.P., Hindocha, C., Schafer, G., Gardner, C., Curran, H.V., 2018. Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. Translational Psychiatry 8.

Morrison, P.D., Nottage, J., Stone, J.M., Bhattacharyya, S., Tunstall, N., Brenneisen, R., Holt, D., Wilson, D., Sumich, A., McGuire, P., Murray, R.M., Kapur, S., Ffytche, D.H., 2011. Disruption of frontal theta coherence by δ 9-tetrahydrocannabinol is associated with positive psychotic

symptoms. Neuropsychopharmacology 36, 827-836.

Morrison, P.D., Zois, V., McKeown, D.A., Lee, T.D., Holt, D.W., Powell, J.F., Kapur, S., Murray, R.M., 2009. The acute effects of synthetic intravenous 9- tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychological Medicine 39, 1607-1616.

Müller-Vahl, K.R., Koblenz, A., Jöbges, M., Kolbe, H., Emrich, H.M., Schneider, U., 2001. Influence of treatment of Tourette Syndrome with Δ9-tetrahydrocannabinol (Δ9-THC) on neuropsychological performance. Pharmacopsychiatry 34, 19-24.

Naef, M., Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L., Zbinden, A., Brenneisen, R., 2003. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain 105, 79-88.

Nicholson, A.N., Turner, C., Stone, B.M., Robson, P.J., 2004. Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. Journal of Clinical Psychopharmacology 24, 305-313.

O'Leary, D.S., Block, R.I., Koeppel, J.A., Schultz, S.K., Magnotta, V. A., Ponto, L.B., Watkins, G.L., Hichwa, R.D., 2007. Effects of smoking marijuana on focal attention and brain blood flow. Human Psychopharmacology-Clinical and Experimental 22, 135-148.

O'Leary, D.S., Block, R.I., Turner, B.M., Koeppel, J., Magnotta, V.A., Ponto, L.B., Watkins, G.L., Hichwa, R.D., Andreasen, N.C., 2003. Marijuana alters the human cerebellar clock. Neuroreport 14, 1145-1151.

Pabon, E., de Wit, H., 2019. Developing a phone-based measure of impairment after acute oral Δ9-tetrahydrocannabinol. Journal of Psychopharmacology 33, 1160-1169.

Ramaekers, J.G., Kauert, G., Theunissen, E.L., Toennes, S.W., Moeller, M.R., 2009. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Journal of Psychopharmacology 23, 266-277.

Ramaekers, J.G., Kauert, G., van Ruitenbeek, P., Theunissen, E.L., Schneider, E., Moeller, M.R., 2006. High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology 31, 2296-2303.

Ramaekers, J.G., Robbe, H.W.J., O'Hanlon, J.F., 2000. Marijuana, alcohol and actual driving performance. Human Psychopharmacology-Clinical and Experimental 15, 551-558.

Ramaekers, J.G., van Wel, J.H., Spronk, D., Franke, B., Kenis, G., Toennes, S.W., Kuypers, K.P.C., Theunissen, E.L., Stiers, P., Verkes, R.J., 2016a. Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes. Brain Imaging and Behavior 10, 1254-1263.

Ramaekers, J.G., van Wel, J.H., Spronk, D.B., Toennes, S.W., Kuypers, K.P.C., Theunissen, E.L., Verkes, R.J., 2016b. Cannabis and tolerance: acute drug impairment as a function of cannabis use history. Scientific Reports 6.

Ranganathan, M., De Aquino, J.P., Cortes-Briones, J.A., Radhakrishnan, R., Pittman, B., Bhakta, S., D'Souza, D.C., 2019. Highs and lows of cannabinoid-dopamine interactions: effects of genetic variability and pharmacological modulation of catechol-O-methyl transferase on the acute response to delta-9-tetrahydrocannabinol in humans. Psychopharmacology 236, 3209-3219.

Ranganathan, M., Sewell, R.A., Carbuto, M., Elander, J., Schnakenberg, A., Radhakrishnan, R., Pittman, B., D'Souza, D.C., 2014. Effects of Δ9-tetrahydrocannabinol in individuals with a familial vulnerability to alcoholism. Psychopharmacology 231, 2385-2393.

Ronen, A., Chassidim, H.S., Gershon, P., Parmet, Y., Rabinovich, A., Bar-Hamburger, R., Cassuto, Y., Shinar, D., 2010. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accident Analysis and Prevention 42, 1855-1865.

Ronen, A., Gershon, P., Drobiner, H., Rabinovich, A., Bar-Hamburger, R., Mechoulam, R., Cassuto, Y., Shinar, D., 2008. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. Accident Analysis and Prevention 40, 926-934.

Roser, P., Gallinat, J., Weinberg, G., Juckel, G., Gorynia, I., Stadelmann, A.M., 2009. Psychomotor performance in relation to acute oral administration of Δ 9-tetrahydrocannabinol and standardized cannabis extract in healthy human subjects. European archives of psychiatry and clinical neuroscience 259, 284.

Roser, P., Juckel, G., Rentzsch, J., Nadulski, T., Gallinat, J., Stadelmann, A.M., 2008. Effects of acute oral Δ9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. European Neuropsychopharmacology 18, 569-577.

Schlienz, N.J., Spindle, T.R., Cone, E.J., Herrmann, E.S., Bigelow, G. E., Mitchell, J.M., Flegel, R., LoDico, C., Vandrey, R., 2020. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug and Alcohol Dependence, 107969.

Schoedel, K.A., Szeto, I., Setnik, B., Sellers, E.M., Levy-Cooperman, N., Mills, C., Etges, T., Sommerville, K., 2018. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. Epilepsy & Behavior 88, 162-171.

Sewell, R.A., Schnakenberg, A., Elander, J., Radhakrishnan, R., Williams, A., Skosnik, P.D., Pittman, B., Ranganathan, M., D'Souza, D. C., 2013. Acute effects of THC on time perception in frequent and infrequent cannabis users. Psychopharmacology 226, 401-413.

Spindle, T.R., Cone, E.J., Goffi, E., Weerts, E.M., Mitchell, J.M., Winecker, R.E., Bigelow, G.E., Flegel, R.R., Vandrey, R., 2020. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug and Alcohol Dependence, 107937.

Spindle, T.R., Cone, E.J., Schlienz, N.J., Mitchell, J.M., Bigelow, G.E., Flegel, R., Hayes, E., Vandrey, R., 2018. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis A Crossover Trial. Jama Network Open 1.

Spronk, D.B., Van der Schaaf, M.E., Cools, R., De Bruijn, E.R.A., Franke, B., van Wel, J.H.P., Ramaekers, J.G., Verkes, R.J., 2016. Acute effects of cocaine and cannabis on reversal learning as a function of COMT and DRD2 genotype. Psychopharmacology 233, 199-211.

Sugarman, D.E., Poling, J., Sofuoglu, M., 2011. The safety of modafinil in combination with oral δ9- tetrahydrocannabinol in humans. Pharmacology Biochemistry and Behavior 98, 94-100.

Theunissen, E.L., Heckman, P., Perna, E., Kuypers, K.P.C., Sambeth, A., Blokland, A., Prickaerts, J., Toennes, S.W., Ramaekers, J.G., 2015. Rivastigmine but not vardenafil reverses cannabis-induced impairment of verbal memory in healthy humans. Psychopharmacology 232, 343-353.

Tunbridge, E.M., Dunn, G., Murray, R.M., Evans, N., Lister, R., Stumpenhorst, K., Harrison, P.J., Morrison, P.D., Freeman, D., 2015. Genetic moderation of the effects of cannabis: Catechol-O-methyltransferase (COMT) affects the impact of δ9-tetrahydrocannabinol (THC) on working memory performance but not on the occurrence of psychotic experiences. Journal of Psychopharmacology 29, 1140-1151.

van den Elsen, G.A.H., Tobben, L., Ahmed, A.I.A., Verkes, R.J., Kramers, C., Marijnissen, R.M., Rikkert, M., van der Marck, M.A., 2017. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: A randomised controlled crossover trial. Journal of Psychopharmacology 31, 184-191.

Van Wel, J.H.P., Kuypers, K.P.C., Theunissen, E.L., Toennes, S.W., Spronk, D.B., Verkes, R.J., Ramaekers, J.G., 2013. Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. British Journal of Pharmacology 170, 1410-1420.

Veldstra, J.L., Bosker, W.M., de Waard, D., Ramaekers, J.G., Brookhuis, K.A., 2015. Comparing treatment effects of oral THC on simulated and on-the-road driving performance: testing the validity of driving simulator drug research. Psychopharmacology 232, 2911-2919.

Wallace, M.S., Marcotte, T.D., Umlauf, A., Gouaux, B., Atkinson, J.

H., 2015. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. Journal of Pain 16, 616-627.

Weinstein, A., Brickner, O., Lerman, H., Greemland, M., Bloch, M., Lester, H., Chisin, R., Sarne, Y., Mechoulam, R., Bar-Hamburger, R., Freedman, N., Even-Sapir, E., 2008. A study investigating the acute dose-response effects of 13 mg and 17 mg Δ 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. Journal of Psychopharmacology 22, 441-451.