# Opioids, Overdoses, and Cannabis: Is Marijuana An Effective Therapeutic Response to the Opioid Abuse Epidemic?

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ABSTRACT

*Drug overdoses fatalities in America, particularly ones attributable to opioid use, outpace most other preventable causes of death. So far, efforts to dissuade parties from using opioids and to disrupt the supply of that drug have not reduced the number of fatalities. To address that problem, several commentators have argued that we should legalize marijuana use as a legitimate analgesic substitute for opioids. The argument is that marijuana can alleviate pain without posing a risk of overdose, because there are few receptors for marijuana's constituents in the brain region responsible for autonomic control of respiration. That suggestion, however, is an unsound one. Marijuana's analgesic effects are not sufficiently powerful to palliate acute pain. Marijuana is also not a reasonable analgesic for chronic pain, for several reasons. For example, a recent, long-term, comprehensive longitudinal study found that participants prescribed opioids, of which 24% also used cannabis daily or less frequently, reported greater pain severity and pain interference (viz., pain effects on sleep, working ability, daily living, social interactions), lower pain self-efficacy, and higher levels of generalized anxiety disorder than those not using cannabis. Moreover, individuals who used marijuana on a near-daily basis were less likely to discontinue opioid use than participants who abstained from cannabis use. Use of marijuana during opioid treatment therefore increases the risk that opioid treatment will be unsuccessful. While further research someday might discover that one or more of marijuana's constituents could*

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*serve as a treatment for long-term chronic pain, there is no such evidence today.*

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Over the last decade, America has witnessed an increase in drug overdose deaths in numbers partaking of Biblical proportions. As one physician put it, "The proliferation of opioid use in the United States is called an epidemic, but it more resembles metastatic cancer."[1]

Consider the numbers involved. According to the Centers for Disease Control and Prevention, from 1999 to 2017 the age adjusted rate of fatal drug overdoses jumped from 6.1 to 21.7 per 100,000 people, with the last four years showing the greatest annual increases.[2] The rate of drug overdose deaths involving synthetic opioids (other than methadone) such as fentanyl increased from 0.3 per 100,000 people in 1999 to 9.0 in 2017,[3] To put those numbers into perspective, the total number of fatal drug overdoses—more than 630,000 people—exceeds the number of deaths America suffered in World Wars I and II combined.[4] Or consider that in 2017 alone there were more than 70,000 drug overdose fatalities, a number greater than the number of people killed by firearms (homicide and suicide), or the number of soldiers who died in the Korean War.[5] In 2016, one person died, on average, every nine minutes.[6] Early estimates by the Centers for Disease Control and Prevention ("CDC") for drug overdose deaths in 2017—70,237—are grim.[7] The number of deaths due to drug overdoses now exceeds the number of deaths attributable to motor vehicle accidents, suicide, and gunshots.[8] To place the current situation in context, most major categories of accidental deaths have declined since 1900. Drug overdose deaths are the notable exception.[9]

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1. David Brown, *Opioids and Paternalism*, AM. SCHOLAR 22–23 (2017).

2. HOLLY HEDEGAARD ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., DRUG OVERDOSE DEATHS IN THE UNITED STATES, 1999–2017, at 1 (2018); *id.* at 1-2 ("The rate increased on average by 10% per years from 1999 through 2006, by 3% per year from 2006 through 2014, and by 16% per year from 2014 through 2017.").

3. *Id.* at 4; *id.* ("The rate increased on average by 8% per year from 1999 through 2013 and by 71% per year from 2013 through 2017.").

4. *Id.* at 1. Approximately 521,915 American military personnel died in the two world wars. Megan Crigger & Lauren Santhanam, *How Many Americans Have Died in U.S. Wars?*, PBS NEWS HOUR (May 24, 2015), https://www.pbs.org/newshour/nation/many-americans-died-u-s-wars [https://perma.cc/WP53-6S57].

5. 54,266 military personnel died during the Korean War. Crigger & Santhanam, *supra* note 4; CTRS. FOR DISEASE CONTROL & PREVENTION, FATAL INJURY REPORTS, NAT'L, REGIONAL AND STATE, 1981–2016 (2017) (reporting 38,658 firearm deaths).

6. *See* HOLLY HEDEGAARD ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., DRUG OVERDOSE DEATHS IN THE UNITED STATES, 1999–2016, at 5 (2017).

7. OFFICE OF NAT'L DRUG CONTROL POL'Y, NAT'L DRUG CONTROL STRATEGY 1 (Jan. 2019).

8. David Powell et al., *Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers?*, 58 J. HEALTH ECON. 29, 29 (2018).

9. STEVEN PINKER, ENLIGHTENMENT NOW: THE CASE FOR REASON, SCIENCE, HUMANISM, AND PROGRESS 242 Fig. 12-6 (2018).

A large influx of federal funds to support research on safer alternatives to conventional opioids is underway, but the timeline for candidate medications to emerge and receive approval by the Food and Drug Administration ("FDA") remains uncertain. In the meantime, Congress, President Donald Trump, federal agencies such as the CDC, the states, and private organizations have taken or recommended a variety of different steps to reduce the carnage, such as increased use of naloxone, an opioid antagonist that can reverse an overdose and save the user's life if it is administered in a timely manner.[10] There is widespread support for the use of that drug as an immediate treatment of someone who has overdosed on opioids, as well as the use of drugs such as methadone or buprenorphine as long-term treatments for opioid dependence.[11] In the hope of ending the epidemic of opioid-induced deaths, some people have suggested addressing this new problem with an old drug: marijuana.

*Marijuana* is a generic term used to denote psychoactive preparations of the cannabis plant. Cannabis is the designation name for the plants *Cannabis sativa*, *Cannabis indica* and, of minor significance, *Cannabis ruderalis*. By contrast, the term *cannabinoids* refers to a class of diverse, biologically active chemical compounds that act on particular cell receptors to modulate the release of neurotransmitters in the brain. The composition, bioavailability, pharmacodynamics (a drug's effect on the body), and pharmacokinetics (the body's effect on a drug) of

10. *See, e.g.*, The Comprehensive Addiction and Recovery Act, Pub. L. No. 114-198, 130 Stat. 695 (2016) (codified in scattered sections of Title 42) (authorizes drug prevention and treatment programs); THE PRESIDENT'S COMM'N ON COMBATING DRUG ADDICTION AND THE OPIOID CRISIS, FINAL REPORT (2017); DEBORAH DOWELL ET AL., CTRS. FOR DISEASE CONTROL & PREVENTION, CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN—UNITED STATES, 2016 (2016); NAT'L ACAD. SCIS., PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE (2017); Richard S. Larson & Halena M. Gazelka, *Debate—Should the Government Limit a Physician's Ability to Prescribe Opioids?*, WALL ST. J., June 24, 2018, https://www.wsj.com/articles/should-the-government-limit-a-physicians-ability-to-treat-patients-with-opioids-1529892300?mod=article_inline [https://perma.cc/QK3D-LP3W]; Betsy McKay, *New CDC Director Targets Opioids, Suicide and Pandemics*, WALL ST. J., June 25, 2018, https://www.wsj.com/articles/new-cdc-director-targets-opioids-suicide-and-pandemics-1529931600?mod=searchresults&page=1&pos=1 [https://perma.cc/C2FE-YSGK]; Kristina Peterson & Stephanie Armour, *Opioid vs. Crack: Congress Reconsiders Its Approach to Drug Epidemic*, WALL ST. J., May 25, 2018, https://www.wsj.com/articles/opioid-v-crack-congress-reconsiders-its-approach-to-drug-epidemic-1525518000 [https://perma.cc/SC3B-222U].

11. *See, e.g.*, OFFICE OF THE SURGEON GEN., U.S. DEP'T OF HEALTH & HUMAN SERVS., SURGEON GENERAL'S ADVISORY ON NALOXONE AND OPIOID OVERDOSE (2018), https://www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html [https://perma.cc/ES2B-7YVF]; Office of the Surgeon Gen., U.S. Dep't of Health & Human Servs., *Surgeon General Releases Advisory on Naloxone, an Opioid Overdose-Reversing Drug* (Apr. 5, 2018), https://www.hhs.gov/about/news/2018/04/05/surgeon-general-releases-advisory-on-naloxone-an-opioid-overdose-reversing-drug.html [https://perma.cc/TNS3-FS68]; Margaret A. Maglione et al., *Effects of Medication Assisted Treatment (MAT) for Opioid Use Disorder on Functional Outcomes: A Systematic Review*, 89 J. SUBSTANCE ABUSE TREATMENT 28 (2018); Roger D. Weiss & Vinod Rao, *The Prescription Opioid Addiction Treatment Study: What Have We Learned*, 173 DRUG & ALCOHOL DEPENDENCY S48 (2017).

botanical cannabis differ from those of extracts of purified individual cannabinoids.[12]

The issue of whether cannabis or one of its cannabinoids has legitimate use as a substitute for, or adjunct to, opiate-based pain treatment has been the subject of discussion in the public media,[13] debate in policy forums,[14] and investigation in

12. There are more than 700 known constituents of cannabis and more than 100 known cannabinoids. Cannabinoids are basically derived from three sources: (a) phytocannabinoids are cannabinoid compounds produced by plants *Cannabis sativa* or *Cannabis indica*; (b) endocannabinoids, which are neurotransmitters produced in the brain or in peripheral tissues and act at cannabinoid or other receptors; and (c) synthetic cannabinoids, synthesized in the laboratory, are structurally analogous or similar to phytocannabinoids or endocannabinoids and may act by similar or different biological mechanisms. Seddon R. Savage et al., *Cannabis in Pain Treatment: Clinical and Research Considerations*, 17 J. PAIN 654, 656 (2016).

13. *See, e.g.*, Richard Boxer, *Can Marijuana Alleviate the Opioid Crisis?*, WALL ST. J., Nov. 19, 2017, https://www.wsj.com/articles/can-marijuana-alleviate-the-opioid-crisis-1511104543 [https://perma.cc/KBV3-AD78]; Ike Brannon, *Legalize Marijuana and Reduce Deaths from Drug Abuse*, HILL, July 8, 2016, http://thehill.com/blogs/pundits-blog/healthcare/286965-legalize-marijuana-and-reduce-deaths-from-drug-abuse [https://perma.cc/BKQ2-PT56]; Lindsay Carlton, *Will Medical Marijuana Replace Opioids in the War on Cancer?*, FOX NEWS, June 11, 2018, http://www.foxnews.com/health/2018/06/11/will-medical-marijuana-replace-opioids-in-war-on-cancer.html [https://perma.cc/LM2W-4NBY]; Richard A. Friedman, *Marijuana Can Save Lives*, N.Y. TIMES, Feb. 8, 2018, https://www.nytimes.com/2018/02/08/opinion/marijuana-opiates-jeff-sessions.html [https://perma.cc/GS5R-9AWY]; Richard Harris, *Opioid Use Lower in States that Eased Marijuana Laws*, NPR (Apr. 2, 2018), https://www.npr.org/sections/health-shots/2018/04/02/598787768/opioid-use-lower-in-states-that-eased-marijuana-laws [https://perma.cc/AZ5N-3HTJ]; Liam Mannix, *In Major Study, Cannabis Shows No Benefit for Chronic Pain*, SYDNEY MORNING HERALD, July 3, 2018, https://www.smh.com.au/national/in-major-study-cannabis-shows-no-benefit-for-chronic-pain-20180702-p4zp0z.html [https://perma.cc/ETD6-WZ6R]; Mark Lieber, *Marijuana Legalization Could Help Offset Opioid Epidemic, Studies Find*, CNN (Apr. 26, 2018), https://www.cnn.com/2018/04/02/health/medical-cannabis-law-opioid-prescription-study/index.html [https://perma.cc/DTZ2-RCTE]; German Lopez, *Medical Marijuana May Help Combat the Opioid Crisis. But There Are Better Solutions*, VOX (Apr. 30, 2018), https://www.vox.com/policy-and-politics/2018/4/30/17302692/opioid-epidemic-medical-marijuana-painkiller [https://perma.cc/35AL-NFU2]; Shefali Luthra, *After Medical Marijuana Legalized, Medicare Prescriptions Drop for Many Drugs*, NPR (July 6, 2016), https://www.npr.org/sections/health-shots/2016/07/06/484977159/after-medical-marijuana-legalized-medicare-prescriptions-drop-for-many-drugs [https://perma.cc/PSB3-BPUZ]; Dean Olsen, *Could Medical Marijuana Help Fight Opioid Abuse? It's Complicated*, STATE J.-REG. (May 30 2018), http://www.sj-r.com/news/20180526/could-medical-marijuana-help-fight-opioid-abuse-its-complicated [https://perma.cc/LJC9-TC5N]; Denise Thompson, *Could Medical Marijuana Help Curb the Opioid Crisis?*, CBS NEWS (Apr. 3, 2018), https://www.cbsnews.com/news/could-medical-marijuana-help-curb-the-opioid-crisis/ [https://perma.cc/Y9AD-6PXR]; Sarah Zhang, *Patients Are Ditching Opioid Pills for Weed. Can Marijuana Help Solve the Opioid Epidemic?*, ATLANTIC, Feb. 2, 2017, https://www.theatlantic.com/health/archive/2017/02/marijuana-cannabinoids-opioids/515358/ [https://perma.cc/A6UX-3R43]; *Can Medical Marijuana Help Combat Illinois' Opioid Crisis?*, U.S. NEWS & WORLD REP. (June 2, 2018), https://www.usnews.com/news/best-states/illinois/articles/2018-06-02/can-medical-marijuana-help-combat-illinois-opioid-crisis.

14. *See, e.g.*, Philippe Lucas & Zach Walsh, *Medical Cannabis Access, Use, and Substitution for Prescription Opioids and Other Substances: A Survey of Authorized Medical Cannabis Patients*, 42 INT'L J. OF DRUG POL'Y 30 (2017); Philippe Lucas, *Rationale for Cannabis-Based Interventions in the Opioid Overdose Crisis*, 14 HARM REDUCTION J. 1 (2017); Powell et al., *supra* note 8, at 30; Rhet Smith, *The Effects of Medical Marijuana Dispensaries on Adverse Opioid Outcomes*, SOC. SCI. RES. NETWORK (Aug. 3, 2017), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3012381 [https://perma.cc/X73P-GNR8]; Amanda Reiman, *Cannabis as a Substitute for Alcohol and Other Drugs*, 6 HARM REDUCTION J. 35 (2009); Jacob M. Vigil et al., *Associations between Medical Cannabis and Prescription Opioid Use*

the scientific community.[15] Congress has numerous bills under consideration that would enhance the ability of researchers to investigate the potential therapeutic benefits of cannabinoids[16] or would permit marijuana to be used as an analgesic.[17] Before enacting any such legislation, however, it is critical for Congress to carefully evaluate the competing arguments about the potential analgesic benefits of cannabis and cannabinoids.[18]

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in Chronic Pain Patients: A Preliminary Cohort Study, PLOS (Nov. 16, 2017), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0187795 [https://perma.cc/4Z4G-7KFF].

15. *See, e.g.*, DEVAN KANSAGARA ET AL., EVIDENCE-BASED SYNTHESIS PROGRAM, BENEFITS AND HARMS OF CANNABIS IN CHRONIC PAIN OR POST-TRAUMATIC STRESS DISORDER—A SYSTEMATIC REVIEW (2017); Ziva Cooper et al., *Impact of Co-Administration of Oxycodone and Smoked Cannabis on Analgesia and Abuse Liability*, 43 NEUROPSYCHOPHARMACOLOGY 2046, 2050–51 (2018) ("Preclinical and population findings provide a strong signal for then potential opioid-sparing effects of cannabinoids."); Wayne Hall et al., *It Is Premature to Expand Access to Medical Cannabis in Hopes of Solving the US Opioid Crisis*, 113 ADDICTION 987 (2018); Marie J. Hayes & Mark S. Brown, *Legalization of Medical Marijuana and Incidence of Opioid Mortality*, 174 JAMA INTERNAL MED. 1673, 1673 (2014); Andrew J. Saxon & Kendall C. Browne, *Marijuana Not Ready for Prime Time as an Analgesic*, 36 GEN. HOSP. PSYCHIATRY 4, 5 (2014); Barth Wisley et al., *Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain*, 14 J. PAIN 136 (2013).

16. *See, e.g.*, The Medical Cannabis Research Act of 2019, H.R. 601, 116th Cong. (2019) (expanding the ability of researchers to investigate the potential medical benefits of marijuana).

17. *See, e.g.*, The Sensible Enforcement of Cannabis Act of 2019, H.R. 493, 116th Cong. (2019) (directing the U.S. Attorney General not to bring a criminal prosecution under the federal Controlled Substances Act "for any conduct that (1) concerns marijuana for medicinal or recreational use; and (2) is authorized by the laws of the State involved).

18. The literature on the two sides of this debate almost outnumbers the grains of sand on the beach. For a sample, see OFF. OF NAT'L DRUG CONTROL POLICY, MARIJUANA MYTHS AND FACTS: THE TRUTH BEHIND 10 POPULAR MISCONCEPTIONS (2014); U.S. COMM'N ON MARIJUANA & DRUG ABUSE, MARIJUANA: A SIGNAL MISUNDERSTANDING (1972); WILLIAM J. BENNETT & ROBERT A. WHITE, GOING TO POT: WHY THE RUSH TO LEGALIZE MARIJUANA IS HARMING AMERICA (2015); ALEX BERENSON, TELL YOUR CHILDREN: THE TRUTH ABOUT MARIJUANA, MENTAL ILLNESS, AND VIOLENCE (2018); JONATHAN P. CAULKINS ET AL., MARIJUANA LEGALIZATION: WHAT EVERYONE NEEDS TO KNOW (2d ed. 2016) [hereinafter CAULKINS ET AL., MARIJUANA LEGALIZATION]; JONATHAN CAULKINS ET AL., RECONSIDERING MARIJUANA LEGALIZATION: INSIGHTS FOR VERMONT AND OTHER JURISDICTIONS (2015); MITCH EARLEYWINE, UNDERSTANDING MARIJUANA: A NEW LOOK AT THE SCIENTIFIC EVIDENCE (2002); WAYNE HALL & ROSALIE LICCARDO PACULA, CANNABIS USE AND DEPENDENCE: PUBLIC HEALTH AND PUBLIC POLICY (2003); INST. OF MEDICINE, MARIJUANA AND MEDICINE: ASSESSING THE SCIENCE BASE (Janet E. Joy et al. eds., 1999) [hereinafter ASSESSING THE SCIENCE BASE]; KEVIN P. HILL, MARIJUANA: THE UNBIASED TRUTH ABOUT THE WORLD'S MOST POPULAR WEED (2015); MARK A.R. KLEIMAN, MARIJUANA: COSTS OF ABUSE, COSTS OF CONTROL (1989); ROBIN ROOM ET AL., CANNABIS POLICY: BEYOND STALEMATE (2010); KEVIN A. SABET, REEFER SANITY: SEVEN GREAT MYTHS ABOUT MARIJUANA (rev. ed. 2018); Jonathan Caulkins, *The Real Dangers of Marijuana*, NAT'L AFFS. (2016); https://www.nationalaffairs.com/publications/detail/the-real-dangers-of-marijuana [https://perma.cc/3LAH-B9LW]; Alex Kreit, *Beyond the Prohibition Debate: Thoughts on the Federal Drug Laws in an Age of State Reforms*, 13 CHAPMAN L. REV. 555 (2010); Wayne Hall, *What Has Research Over the Past Two Decades Revealed About the Adverse Health Effects of Recreational Cannabis Use?*, 110 ADDICTION 19 (2014); Herbert Moskowitz, *Marihuana and Driving*, 17 ACCIDENT ANALYSIS & PREVENTION 323 (1985); Rosalie Liccardo Pacula & Eric L. Sevigny, *Marijuana Liberalization Policies: Why We Can't Learn Much from Policy Still in Motion*, 33 J. POL'Y ANALYSIS & MGMT. 212 (2014); *compare* Kevin Sabet, *Marijuana and Legalization Impacts*, 23 BERKELEY J. CRIM. L. 84 (2018), *with* Tamar Todd, *The Benefits of Marijuana Legalization and Regulation*, 23 BERKELEY J. CRIM. L. 99 (2018); *see generally* Paul J. Larkin, Jr., *Introduction to a Debate: "Marijuana: Legalize, Decriminalize, or Leave the Status Quo in Place?*," 23

Part I describes the epidemic of opioid-caused overdose fatalities. Part II summarizes how the state and federal governments have regulated cannabis for most of the twentieth century. Part III summarizes the argument why marijuana is a reasonable analgesic substitute for opioids. Part IV then approaches this issue from the opposite side, explaining why, although there might be legitimate therapeutic uses for isolated cannabinoids, the marijuana plant itself likely will never become a legitimate, scientifically accepted analgesic, particularly when smoked. Part V then asks where we go from here. It concludes that Congress should remove any remaining arbitrary or unreasonable restraints on scientific research into the therapeutic potential of marijuana and cannabinoids

## I. THE EPIDEMIC OF OPIOID-CAUSED FATAL OVERDOSES

Opioids are a class of naturally derived, semi-synthetic, or synthetic drugs that target three types of opioid receptors in the brain, the mu (μ), kappa ($\kappa$), and delta ($\delta$) receptors. These receptors mediate a range of physiological and pharmacological effects, including analgesia.[19] Used on a short-term basis, opioids are extremely effective for patients who suffer moderate to severe acute pain stemming from a major injury, surgery, a gunshot wound, or the end stages of terminal cancer.

Opioid prescription was largely restricted to those limited applications for decades after the first wave of iatrogenic (treatment-caused) opioid addiction, which started in the nineteenth century and persisted into the early part of the twentieth century. Beginning in the 1990s, however, physicians increasingly prescribed opioids for treatment of chronic pain, an affliction that deprives millions of Americans of a satisfying quality of life. The resulting opioid crisis is costing the economy between (an estimated) $78.5 and $500 billion dollars annually.[20]

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BERKELEY J. CRIM. L. 73, 75–78 (2018) (summarizing the competing arguments and collecting authorities).

19. Technically, the term "opioids" refers to two types of drugs. "Opiates" are a class of analgesic drugs developed from poppies (for example, morphine and codeine), while "opioids" is used to describe those drugs as well as chemically synthesized versions that can be manufactured entirely in a laboratory (for example, fentanyl). JERROLD S. MEYER & LINDA F. QUENZER, PSYCHOPHARMACOLOGY: DRUGS, THE BRAIN, AND BEHAVIOR 306 n.1 (2d ed. 2018); Paul J. Larkin, Jr., Robert L. DuPont & Bertha K. Madras, *The Need to Treat Driving under the Influence of Drugs as Seriously as Driving under the Influence of Alcohol*, HERITAGE FOUND., BACKGROUNDER No. 3316, at 8 n.18 (May 16, 2018), https://www.heritage.org/sites/default/files/2018-05/BG3316_1.pdf [https://perma.cc/5U2W-FPZK]. Hereinafter we will use the term "opioids" to refer to both types of drugs.

20. COUNCIL OF ECON. ADVISORS, THE UNDERESTIMATED COST OF THE OPIOID CRISIS (2017), https://www.whitehouse.gov/briefings-statements/cea-report-underestimated-cost-opioid-crisis/ [https://perma.cc/4XPC-349K]; Kevin Boehnke et al., *Medical Cannabis Use Is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain*, 17 J. PAIN 739, 739 (2016) (noting that chronic pain affects more than 100 million Americans each year and imposes direct and indirect annual costs of up to $635 billion); AMY S. BOHNERT, MICH. INST. HEALTH CARE POLICY & INNOVATION, REDUCING UNINTENTIONAL OPIOID OVERDOSE BY IMPROVING PRESCRIBING PRACTICES (2014), https://ihpi.umich.edu/sites/default/files/ihpi-bohnert-research%20-%20final.pdf [https://perma.cc/BW4P-FQML] (noting an estimate that 100 million Americans suffer from chronic pain); Richard L. Nahin, *Estimates of Pain Prevalence and Severity in Adults: United States,*

Unfortunately, a mistaken perception that long-term opioid use is benign and therefore can be liberally prescribed for myriad pain conditions, has led to unintended (albeit historically predictable) worse consequences than the problem of unaddressed pain that opioids were supposed to remedy.

There are potentially severe downsides to the long-term use of opioids. The principal risk for individuals, as medicine discovered late in the nineteenth century, is that opioids are highly addictive in susceptible individuals, with the added risk of an overdose. The euphoric effect of opioids overwhelms the brain's reward centers, leading to continued opioid use and, ultimately, physical dependence or addiction. Once a person becomes addicted, quitting is a very difficult process. Unless they are aided by other medications, individuals suffering from withdrawal experience a miserable, painful period that can set in hours after taking the last dose and can last for a week or more.[21] What is worse, someone who uses opioids for a long time, such as someone suffering from chronic back pain, can develop a tolerance to the drug, requiring ever-increasing dosages, or a more powerful opioid, to receive the same relief.[22] Far worse still is the fact that high doses of opioids can lead to a fatal overdose because opioid receptors are abundant in the brainstem region responsible for autonomic respiration. Overactivity of the large number of *mu* opioid receptors in the brainstem region can suppress breathing and lower blood oxygen levels, leading to coma and death.[23] The principal risk for a society awash with opioids, as we now have painfully learned, is a contemporary public health nightmare: the massive number of fatalities that opioid abuse can generate.

A range of solutions is needed to address this public health disaster, including reducing the number of prescription opioids.[24] Oversupply of prescription drugs was the root cause of the current opioid epidemic. By 2013, opioid analgesics caused more deaths (over 16,200 in 2013) than all illicit drugs combined (14,775).[25] By 2016, 11.8 million people reportedly misused prescription opioids, 2.1 million suffered from a "substance use disorder," with half that many self-reporting a heroin-use disorder.[26] In 2005, 90% of people in treatment for heroin

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2012, 18 J. PAIN 769 (2015); Curtis Florence et al., *The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013*, 54 MED. CARE 901 (2016).

21. *See, e.g.*, JOHN BRICK & CARLTON K. ERICKSON, DRUGS, THE BRAIN, AND BEHAVIOR: THE PHARMACOLOGY OF DRUG USE DISORDERS 91 & tbl. 8.3 (2d ed. 2013) (withdrawal symptoms include goose bumps, achiness, weakness, irritability, insomnia, alternating chills and sweating, hypersensitivity, cramps, diarrhea, emesis, and "a spastic jerky movement" that has earned the moniker "kicking the habit").

22. MEYER & QUENZER, *supra* note 19, at 325–26, 419–21.

23. *Id.* at 309.

24. *See* THE PRESIDENT'S COMM'N ON COMBATING DRUG ADDICTION AND THE OPIOID CRISIS, *supra* note 10.

25. Rose A. Rudd et al., *Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014*, 64 MORBIDITY & MORTALITY WKLY. REP. 1378 (2016).

26. SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADM'N, U.S. DEP'T OF HEALTH & HUMAN SERVS., KEY SUBSTANCE USE & MENTAL HEALTH INDICATORS IN THE UNITED STATES: RESULTS FROM THE 2016 NATIONAL SURVEY ON DRUG USE & HEALTH (2017).

addiction reported prescription opioids as their first exposure to that class of drugs. By 2015, that proportion had declined to 67%, reflecting the growing use of illicit, possibly deadlier opioids such as heroin or fentanyl.[27] The proportion of patients treated with opioids that progress to addiction is unknown,[28] but the consequences of overprescribing—misuse by patients and diversion to and misuse by unintended populations—is a clear danger.

There is a pressing need to find long-term, non-addictive, analgesic alternatives to opioids for chronic pain sufferers in addition to the twenty or so drugs that currently exist. Also needed is a re-examination of non-opioid treatments for chronic pain.[29] Remarkably, randomized controlled clinical trials comparing opioids with non-opioids for chronic pain are uncommon. But one such well-executed study recently showed that among randomized patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain, pain intensity was significantly improved in the non-opioid group compared with the opioid group treated over twelve months, and adverse medication-related symptoms were significantly more common in the opioid group. The authors of the study concluded that treatment with opioids was not superior to treatment with non-opioid medications for improving pain-related function over twelve months and did not support opioid therapy for the conditions suffered by participants in the study.[30] Further research and study might prove fruitful.

## II. OF OLD WINE AND NEW BOTTLES

Marijuana served as an ancient medication beginning millennia ago.[31] Today, a number of parties claim that it still has a considerable number of legitimate medicinal uses.[32] At the same time, numerous meta-analyses using rigorous

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27. Theodore J. Cicero et al., *Increased Use of Heroin as an Initiating Opioid of Abuse*, 74 ADDICT BEHAV. 63 (2017).

28. Ajay D. Wasan et al., *Iatrogenic Addiction in Patients Treated for Acute or Subacute Pain: A Systematic Review*, 2 J. OPIOID MGMT. 16 (2006).

29. DOWELL ET AL., *supra* note 10; Yngvild Olsen, *The CDC Guideline on Opioid Prescribing: Rising to the Challenge*, 315 JAMA 1577 (2016); Erin E. Krebs et al., *Effect of Opioid vs. Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial*, 319 JAMA 872 (2018).

30. Krebs et al., *supra* note 29.

31. Archaeological evidence reveals that man-used, naturally growing marijuana more than ten thousand years ago. *See, e.g.*, Sunil K. Aggarwal et al., *Medicinal Use of Cannabis in the United States: Historical Perspectives, Current Trends, and Future Directions*, 5 J. OPIOID MGMT. 153, 153–57 (2009); Alan J. Budney et al., *Cannabis*, *in* LOWINSON & RUIZ'S SUBSTANCE ABUSE: A COMPREHENSIVE TEXTBOOK 214–15 (Pedro Ruiz & Eric Strain eds., 5th ed. 2011); Tod H. Mikuriya, *Marijuana in Medicine: Past, Present, and Future*, 110 CAL. MED. 34 (1969); Solomon H. Snyder, *Foreword* to LESLIE L. IVERSEN, THE SCIENCE OF MARIJUANA 12–13, 17–18, 21–24, 116, 121 (2d ed. 2008).

32. Commonly cited therapeutic uses of cannabis include treatment of chemotherapy-induced nausea and emesis, the neuropathic pain and spasticity caused by multiple sclerosis, and AIDS-induced cachexia. *See, e.g.*, BRITISH MED. ASS'N, THERAPEUTIC USES OF CANNABIS 21–49 (1997); WORLD HEALTH ORG., CANNABIS: A HEALTH PERSPECTIVE AND RESEARCH AGENDA (1997); NAT'L ACAD. OF SCIS., ENG'G, & MED., THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS 54 Tbl. 2-2, 128 Box 4-1 (2017) (listing conditions for which marijuana is a treatment for which there are varying degrees of

standards of proof dispute those conclusions.[33] That debate has continued for more than fifty years without a clear victor.

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scientific support); Gemayel Lee et al., *Medical Cannabis for Neuropathic Pain*, 22 CURRENT PAIN & HEADACHE REP. 8 (2018) ("Nearly 20 years of clinical data supports the short-term use of cannabis for the treatment of neuropathic pain.").

33. *See* BERTHA K. MADRAS, UPDATE OF CANNABIS AND ITS MEDICAL USE (2015) (commissioned monograph to 37th Expert Committee on Drug Dependence, World Health Organization), http://www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf [https://perma.cc/SA4P-SRA6]; *see also*, *e.g.*, J. Aviram & G. Samuelly-Leichtag, *Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*, 20 PAIN PHYSICIAN E755 (2017); David J. DiBenedetto et al., *The Association Between Cannabis Use and Aberrant Behaviors During Chronic Opioid Therapy for Chronic Pain*, 19 PAIN MED. 1997 (2018); Yanju Bao et al., *Complementary and Alternative Medicine for Cancer Pain: An Overview of Systematic Reviews*, EVIDENCE-BASED COMPLEMENTARY & ALT. MED. (Apr. 13, 2014), https://www.hindawi.com/journals/ecam/2014/170396 [https://perma.cc/63EB-YYFU]; Lynneice L. Bowen & Aimee L. McRae-Clark, *Therapeutic Benefit of Smoked Cannabis in Randomized Placebo-Controlled Studies*, 38 PHARMACOTHERAPY 80 (2018); E. Foglia et al., *Cannabis Use and Adherence to Antipsychotic Medication: A Systematic Review and Meta-Analysis*, 47 PSYCHOLOGICAL MED. 1691 (2017); David Gloss & Barbara Vickrey, *Cannabinoids for Epilepsy*, COCHRANE DATABASE SYSTEMATIC REV. (Mar. 5, 2014), https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009270.pub3/media/CDSR/CD009270/CD009270.pdf [https://perma.cc/D3KM-FVBT]; Matt Goldenberg et al., *The Impact of Cannabis and Cannabinoids for Medical Conditions on Health-Related Quality of Life: A Systematic Review and Meta-Analysis*, 174 DRUG ALCOHOL DEPENDENCE 80 (2017); Andrew M. Harrison et al., *Systematic Review of the Use of Phytochemicals for Management of Pain in Cancer Therapy*, 205 BIOMEDICAL RES. INT'L (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630373/pdf/BMRI2015-506327.pdf; Barbara S. Koppel et al., *Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology*, 82 NEUROLOGY 556 (2014); Elizabeth E. Lutge et al., *The Medical Use of Cannabis for Reducing Morbidity and Mortality in Patients with HIV/AIDS*, COCHRANE DATABASE SYSTEMATIC REV. (Apr. 30, 2013), https://www.ncbi.nlm.nih.gov/pubmed/23633327 [https://perma.cc/W8RA-7526]; George G. Mammen et al., *Association of Cannabis with Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies*, 79 J. CLINICAL PSYCHIATRY (2018), https://www.ncbi.nlm.nih.gov/pubmed/29877641 [https://perma.cc/9U4Z-6GP2]; Martin Mücke et al., *Cannabis-Based Medicines for Chronic Neuropathic Pain in Adults*, COCHRANE DATABASE SYSTEMATIC REV. (Mar. 7, 2018), https://www.ncbi.nlm.nih.gov/pubmed/29400010 [https://perma.cc/3YTA-L3SH]; Shannon M. Nugent et al., *The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review*, 167 ANNALS INTERNAL MED. 319 (2017); Maya E. O'Neil et al., *Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder: A Systematic Review*, 167 ANNALS INTERNAL MED. 332 (2017); Pal Pacher et al., *Cardiovascular Effects of Marijuana and Synthetic Cannabinoids: The Good, the Bad, and the Ugly*, 15 NAT. REV. CARDIOLOGY 151 (2018); Kristin Salottolo et al., *The Grass Is Not Always Greener: A Multi-Institutional Pilot Study of Marijuana Use and Acute Pain Management Following Traumatic Injury*, 12 PATIENT SAFETY IN SURGERY 16 (2018); Ilona Shishko et al., *A Review of Medical Marijuana for the Treatment of Posttraumatic Stress Disorder: Real Symptom Re-leaf or Just High Hopes?*, 8 MENTAL HEALTH CLINIC 86 (2018); Renata Solimini et al., *Neurological Disorders in Medical Use of Cannabis: An Update*, 16 CNS & NEUROLOGICAL DISORDERS – DRUG TARGETS 527 (2017); Maria M. Steenkamp et al., *Marijuana and Other Cannabinoids as a Treatment for Posttraumatic Stress Disorder: A Literature Review*, 34 DEPRESSION & ANXIETY 207 (2017); Penny F. Whiting et al., *Cannabinoids for Medical Use: A Systematic Review and Meta-analysis*, 313 JAMA 2456 (2015); Samuel T. Wilkinson et al., *A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications*, 77 J. CLINICAL PSYCHIATRY 1050 (2016); Shane Shucheng Wong & Timothy E. Wilens, *Medical Cannabinoids in Children and Adolescents: A Systematic Review*, 140 PEDIATRICS e20171818 (2017); Vijayshree Yadav et al., *Summary of Evidence-Based Guideline: Complementary and Alternative Medicine in Multiple Sclerosis: Report of the Guideline Development Subcommittee of the American Academy of Neurology*, 82 NEUROLOGY 1083 (2014); *but see* Michael H. Andreae et al.,

For most of the twentieth century, however, marijuana's opponents have won where it counts: in the criminal code. The states and federal government have concluded that marijuana had no legitimate medical use and treated the cultivation, distribution, and possession of marijuana as a crime.[34] For example, in the Controlled Substances Act of 1970,[35] Congress placed marijuana in Schedule I, a category of drugs deemed contraband and outlawed for any therapeutic use because they are dangerous, highly addictive, and offer no therapeutic benefit unavailable through other drugs.[36] The United States also belongs to several international conventions requiring this nation to treat marijuana trafficking as a crime.[37]

Nonetheless, efforts to liberalize the use of cannabis have continued without let-up since the 1960s, and they finally bore fruit in 1996. In that year, California authorized marijuana to be used for various medical purposes by adopting Proposition 215, known as the Compassionate Use Act.[38] Since then, most states have revised their state constitutions or criminal codes to permit marijuana use by

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*Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-Analysis of Individual Patient Data*, 16 J. PAIN 1221 (2015).

34. *See, e.g.*, RICHARD J. BONNIE & CHARLES H. WHITBREAD II, THE MARIJUANA CONVICTION: A HISTORY OF MARIJUANA PROHIBITION IN THE UNITED STATES (1999); MARTIN BOOTH, CANNABIS: A HISTORY (2005). Despite its status as contraband, cannabis is the most frequently used illicit drug in the United States. Wilson M. Compton et al., *Medical Marijuana Laws and Cannabis Use: Intersections of Health and Policy*, 74 JAMA PSYCHIATRY 559, 559 (2017). One estimate is that 40% of Americans have used it. Budney et al., *supra* note 31, at 215.

35. The Controlled Substances Act was enacted as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91–513, 84 Stat. 1236. Under that act, a "controlled substance" is "a drug or other substance, or immediate precursor, included in schedule I, II, III, IV, or V of part B of this title," except for "distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1954." 21 U.S.C. § 802(6) (2012). The Controlled Substances Act incorporates the definition of a "drug" from the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 201(g)(1) (2017).

36. Congress placed marijuana in Schedule I when it enacted the Controlled Substances Act. *See* Alliance for Cannabis Therapeutics v. DEA, 930 F.2d 936, 937 n.1 (D.C. Cir. 1991). Marijuana (and its salts, isomers, and synthetic equivalents) remains on that list today. 21 C.F.R. § 1308.11(d)(31) (2017). Drugs placed on Schedule I are ones found to have no accepted medical use and pose a serious danger of harm and addiction. Physicians cannot prescribe them. Paul J. Larkin, Jr., *Medical or Recreational Marijuana and Drugged Driving*, 52 AM. CRIM. L. REV. 453, 460 & nn.26–27 (2015) [hereafter Larkin, *Drugged Driving*].

37. *See* Single Convention on Narcotic Drugs, Mar. 30, 1961, 18 U.S.T. 1407, *amended by* 1972 Protocol, Mar. 25, 1972, 26 U.S.T. 1439; Convention on Psychotropic Substances, Feb. 21, 1971, 32 U.S.T. 543; United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Dec. 20, 1988, 1582 U.N.T.S. 164.

38. Larkin, *Drugged Driving*, *supra* note 36, at 468. There is considerable reason to believe that the proposition was a disguised effort to take the first step toward marijuana legalization. *Id.* at 510–12. As explained below, accepted standards for medical proof did not support a majority of the listed conditions: "cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, [and] migraine." CAL. HEALTH & SAFETY CODE § 11362.5 (West 2014); *see, e.g.*, NAT'L ACAD. SCIS., *supra* note 32, at 90. The last specified condition—"any other illness for which marijuana provides relief"—is sufficiently capacious to permit a physician to recommend marijuana for a headache.

adults for medical purposes.[39] Some states even authorize adults to use marijuana for recreational purposes. Given the epidemic of fatal opioid overdoses, marijuana's supporters argue, the government should permit marijuana to be used as a long-term palliative for chronic pain.[40]

## III. THE ARGUMENT FOR USING MARIJUANA AS AN ANALGESIC

Proponents claim that marijuana can supply the long-term relief that chronic pain sufferers need. At a minimum, marijuana can serve as the necessary bridge until the discovery of a magic bullet—a safe, long-term, non-addictive analgesic that can alleviate all forms and amounts of pain. The case for legalizing marijuana for analgesic medical use proceeds in five steps.

### *A. Cannabinoids Have Therapeutic Value*

Science has recognized that phyto- and synthetic cannabinoids have therapeutic value.[41] The best proof of that conclusion can be seen in the fact that the FDA has long approved two cannabinoids—dronabinol (or Marinol as capsules, Syndros, as an oral solution), a synthetic form of the psychoactive ingredient in the plant form of marijuana—$\Delta^9$-tetrahydrocannabinol or THC,[42] and nabilone (Cesamet), an analog of THC—for the treatment of chemotherapy-induced nausea and emesis, and as an appetite enhancer to treat AIDS wasting.[43] The FDA recently approved another cannabinoid—cannabidiol (Epidiolex), a nonpsychoactive chemical component of cannabis—for treatment of Lennox-Gastaut

39. Larkin, *Drugged Driving*, *supra* note 36, at 468–69. There is considerable variation among the state regulatory programs. *See* Rosalie L. Pacula et al., *Words Can Be Deceiving: A Review of Variation among Legally Effective Medical Marijuana Laws in the United States*, 7 J. DRUG POL'Y ANALYSIS 1 (2014). The 1996 California law was so open-ended and was applied so broadly that it was tantamount to a recreational use law. *See* CAL. HEALTH & SAFETY CODE § 11362.5 (West 2014) (authorizing marijuana to be used for treatment of "cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, *or any other illness for which marijuana provides relief*") (emphasis added); Larkin, *Drugged Driving*, *supra* note 36, at 510–12; *cf.* Deepak Cyril D'Souza & Mohini Ranganathan, *Medical Marijuana: Is the Cart Before the Horse?*, 313 JAMA 2431, 2431 (2015) (questioning why states authorize medical marijuana for diseases such as psoriasis). Beginning in 2012, eight of those states, including California and the District of Columbia, have gone further by legalizing the possession and recreational use of small amounts of marijuana. Magdalena Cerdá et al., *Association of State Recreational Marijuana Laws with Adolescent Marijuana Use*, 171 JAMA PEDIATRICS 142, 143 (2017).

40. *See, e.g.*, CAULKINS ET AL., MARIJUANA LEGALIZATION, *supra* note 18, at 131–57.

41. *See, e.g.*, Budney et al., *supra* note 31, at 233.

42. NAT'L ACAD. SCIS., *supra* note 32, at 54 tbl. 2-2. The chemical structure of THC closely resembles that of anandamide, an endogenously produced cannabinoid, named after the Sanskrit term "ananda," which means "bliss." MADRAS, *supra* note 33; Maximilian Peters & Raphael Mechoulam, *The Endocannabinoid System*, *in* 2 PROFESSIONAL PERSPECTIVES ON ADDICTION MEDICINE 31, 34–36 (Mark Sanford & Donald Avoy eds., 2009).

43. *See* OFFICE OF THE SURGEON GEN., U.S. DEP'T OF HEALTH AND HUMAN SERVS., FACING ADDICTION IN AMERICA: THE SURGEON GENERAL'S REPORT ON ALCOHOL, DRUGS, AND HEALTH 1–22 (2016); NAT'L ACAD. SCIS., *supra* note 32, at 54 tbl. 2-2; MEYER & QUENZER, *supra* note 19, at 410.

syndrome and Dravet syndrome, two rare, severe forms of epilepsy in children.[44] In announcing the FDA's approval, Commissioner Scott Gottlieb noted, "This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies."[45]

### *B. Neurobiology Has Proved that Humans Are Hardwired to Treat Some Cannabinoids as Analgesics*

Early in the 1990s, scientists discovered that humans have an innate set of cannabinoid signaling systems, involving nerve receptors ($CB_1$, and $CB_2$), and collectively known as the endogenous cannabinoid system, which includes receptors, neurotransmitters to activate them, and an enzyme to terminate signaling. $CB_1$ receptor distribution within the central nervous system is consistent with its role in the control of motor function, cognition, and memory, and appears to mediate most, if not all of the psychoactive effects of THC and THC-related compounds.[46] $CB_1$ receptors are located at sites in the brain associated with pain processing.[47] $CB_2$ receptors are abundantly expressed in peripheral organs with immune function (blood macrophages, spleen, tonsils, thymus, leukocytes, lungs, and testes). The brain also produces endogenous cannabinoids (endocannabinoids), which bind to and activate the cannabinoid receptors.[48] Perhaps in part for that reason, people have used cannabis for centuries to relieve pain.[49]

That discovery also may explain why various scientific analyses—including a 2017 report by the National Academy of Sciences, Engineering, and Medicine on the therapeutic uses of cannabis and cannabinoids—have found that certain individual cannabinoids have an analgesic effect, particularly for various types of neuropathic pain.[50]

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44. Peter Loftus, *FDA Approves First Drug Derived from Marijuana Plant*, WALL ST. J. (June 25, 2018), https://www.wsj.com/articles/fda-approves-first-drug-derived-from-marijuana-plant-1529954791 [http://perma.cc/MB3T-63K2].

45. *Id.*

46. MEYER & QUENZER, *supra* note 19, at 407.

47. *Id.*

48. *Id.*; *see also*, *e.g.*, Benjamin F. Cravatt & Aron H. Lichtman, *The Endogenous Cannabinoid System and Its Role in Nociceptive Behavior*, 61 J. NEUROBIOLOGY 149 (2004); Elizabeth J. Rahn & Andrea G. Hohmann, *Cannabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside*, 6 NEUROTHERAPEUTICS 713, 714 (2009); Savage et al., *supra* note 12, at 656.

49. *See, e.g.*, MEYER & QUENZER, *supra* note 19, at 403; J. Michael Walker et al., *The Neurobiology of Cannabinoid Analgesia*, 65 LIFE SCIS. 665 (1999); *supra* note 32 and accompanying text.

50. *See, e.g.*, OFFICE OF THE SURGEON GEN., *supra* note 43, at 1–2 ("There is a growing body of research suggesting the potential therapeutic value of marijuana's constituent cannabinoid chemicals in numerous health conditions including pain, nausea, epilepsy, obesity, wasting disease, addiction, autoimmune disorders, and other conditions."); NAT'L ACAD. SCIS., *supra* note 32, at 90 ("Conclusion 4-1: There is substantial evidence that cannabis or cannabinoids is an effective treatment for chronic pain in adults."); Ziva D. Cooper et al., *Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana in Daily Marijuana Smokers*, 38 NEUROPSYCHOPHARMACOLOGY 1984 (2013); Jaseena Elikottil et al., *The Analgesic Potential of Cannabinoids*, 5 J. OPIOID MGMT. 341 (2009); Mary E. Lynch

### *C. Cannabis Is a Safer Drug than Any Opioid*

There is no reported case of someone overdosing on cannabis because there are few cannabinoid receptors in the brainstem, which controls involuntary respiration.[51] Plus, the risk of dependence from long-term marijuana use may be less than the comparable risk posed by long-term opioid use. According to a widely quoted 1994 study of comparative lifelong dependence, 23.1% of Americans

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& Fiona Campbell, *Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials*, 72 BRIT. J. CLIN. PHARMACOLOGY 735, 742 (2011) ("In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment for chronic non-cancer (predominantly neuropathic) pain."); Yasmin L. Hurd, *Cannabidiol: Swinging the Marijuana Pendulum from "Weed" to Medication to Treat the Opioid Epidemic*, 40 TRENDS IN NEUROSCIENCES 124 (2017); Sanjeet Narang et al., *Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy*, 9 J. PAIN 254, 261 (2008) ("[D]ronabinol may be a useful adjuvant analgesic for patients with persistent pain in spite of taking stable doses of opioids."); Russell Noyes, Jr. et al., *Analgesic Effect of Delta-9-Tetrahydrocannabinol*, 15 J. CLINICAL PHARMACOLOGY 139, 143 (1975) [hereinafter Noyes et al., *Analgesic Effect of THC*]; Russell Noyes, Jr. et al., *The Analgesic Properties of Delta-9-Tetrahydrocannabinol and Codeine*, 18 CLINICAL PHARMACOLOGY AND THERAPEUTICS 84, 88-89 (1975); Turo J. Nurmikko et al., *Sativex Successfully Treats Neuropathic Pain Characterized by Allodynia: A Randomised, Double-Blind, Placebo-Controlled Clinical Trial*, 133 J. PAIN 210 (2007); Martin Pinsger et al., *Benefits of an Add-On Treatment of Synthetic Cannabinomimetic Nabilone on Patients with Chronic Pain—A Randomized Controlled Trial*, 10 EUROPEAN J. PAIN S163 (2006); Rahn & Hohmann, *supra* note 48; P.J. Robson, *Therapeutic Potential of Cannabinoid Medicines*, 6 DRUG ANALYSIS & TESTING 24 (2014); Whiting et al., *supra* note 33, at 2468 ("There is moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity."); Bart Wilsey et al., *Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain*, 14 J. PAIN 136 (2013); *see also generally* Saxon & Browne, *supra* note 15, at 5 ("Numerous small controlled studies have repeatedly demonstrated that certain cannabinoids do reduce acute and chronic pain when compared to placebo in double-blind designs. Most of these trials have use[d] pharmaceutical forms of cannabinoids, either dronabinol (oral THC), nabilone (an oral, synthetic THC analog) or an extract of plant cannabis containing nearly equal proportions of THC and cannabidiol delivered as an oral mucosal spray, although a few have used smoked or vaporized marijuana."); *but see id.* ("Most of the trials have relatively small sample sizes and used crossover designs over brief periods. One study of an oral mucosal spray did have an open-label extension to 52 weeks with reported continuing benefits. In all the studies, the cannabinoids had a worse side effect profile than the placebo that sometimes included measurable cognitive adverse events. In one study nabilone was less efficacious than dihydrocodeine but had more problematic side effects."). There were problems, however, with some studies used to support marijuana substitution therapy: they had a short duration, the participants were experienced marijuana users, and participants continued to use opioids throughout the short-term protocols. MADRAS, *supra* note 33, at 21–23.

51. *See, e.g.*, IVERSEN, *supra* note 31, at 56; MEYER & QUENZER, *supra* note 19, at 405, 423; J. Michael Bostwick, *The Use of Cannabis for Management of Chronic Pain*, 36 GEN. HOSP. PSYCHIATRY 2, 2 (2014) ("Lethal respiratory suppression by cannabis has never been reported, and there is no phenomenon like the current epidemic of prescription opioid-related deaths attributable to cannabis."); Compton et al., *supra* note 34, at 559 ("Cannabinoid-1 receptors have their highest concentration in the cortex, basal ganglia, hippocampus, and cerebellum, areas involved in decision making and self-regulation, reward and motivation, memory and conditioning, and time-perception and motor coordination, respectively. In the brain, cannabinoid-2 receptors are primarily concentrated in immune cells. . . ."); Rahn & Hohmann, *supra* note 48, at 714 ("Densities of CB1 receptors are low in brainstem sites critical for controlling heart rate and respiration. This distribution explains the low toxicity and absence of lethality after marijuana intoxication."). That fact differentiates marijuana from opioids such as fentanyl, a powerful analgesic that can lead to a cessation of respiration and is a major cause of the overdose deaths America has witnessed over the last few years. *See* THE PRESIDENT'S COMM'N ON COMBATING DRUG ADDICTION AND THE OPIOID CRISIS, *supra* note 10, at 16, 19, 23, 26–27, 29, 32.

who had used heroin became dependent on that drug, while only 9.1% of cannabis users suffered that fate.[52] To be sure, marijuana use presents various health risks,[53] but dying from respiratory cessation is not among them.[54] Accordingly, even if cannabis is not an optimum treatment for chronic pain, it is a far less dangerous alternative than opioids and should be permitted at least until other long-term analgesics can be invented that pose even fewer health risks.

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52. *See, e.g.*, James C. Anthony et al., *Comparative Epidemiology of Dependence on Tobacco, Alcohol, Controlled Substances, and Inhalants: Basic Findings from the National Comorbidity Survey*, 2 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 244, 254–55 (1994); Bostwick, *supra* note 51, at 2 (cannabis poses a lower risk of dependency than opioids). More recent studies reported a higher prevalence of marijuana addiction in the 2000s, ranging from 11–35.6%. *See* Wilson M. Compton et al., *Marijuana Use and Use Disorders in Adults in the USA, 2002–14: Analysis of Annual Cross-Sectional Surveys*, 3 LANCET PSYCHIATRY 954 (2016); Deborah S. Hasin et al., *Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013*, 72 JAMA PSYCHIATRY 1235 (2015).

53. *See, e.g.*, WORLD HEALTH ORG., THE HEALTH AND SOCIAL EFFECTS OF NONMEDICAL CANNABIS USE 15 (2016) ("The daily use of cannabis over years and decades appears to produce persistent impairments in memory and cognition, especially when cannabis use begins in adolescence. . . ."); HALL & PACULA, *supra* note 18, at 78 ("A cannabis dependence syndrome occurs in heavy chronic users of cannabis. Regular cannabis users develop tolerance to THC, some experience withdrawal symptoms on cessation of use, and some report problems controlling their cannabis use. The risk of dependence is about one in ten among those who ever use the drug, between one in five and one in three among those who use cannabis more than a few times, and around one in two among daily users."); MEYER & QUENZER, *supra* note 19, at 422–25; C.H. Ashton, *Adverse Effects of Cannabis and Cannabinoids*, 83 BRITISH J. ANAESTHESIA 637 (1999); Budney et al., *supra* note 31, at 214–16, 227–29; Paul J. Larkin, Jr., *The Problem of "Driving While Stoned" Demands an Aggressive Public Policy Response*, 11 J. DRUG POL'Y ANALYSIS 1 (2018) (describing the problems caused by marijuana-impaired driving); Nora D. Volkow et al., *Adverse Health Effects of Marijuana Use*, 370 NEW ENG. J. MED. 2219 (2014); *Today's Heroin Epidemic Infographics*, CTRS. DISEASE CONTROL & PREVENTION (July 7, 2015), https://www.cdc.gov/vitalsigns/heroin/infographic.html [https://perma.cc/HT34-GDQX] (noting that individuals who are addicted to marijuana are three times as likely to become addicted to heroin); *see generally* Paul J. Larkin, Jr., *Marijuana Edibles and "Gummy Bears"*, 66 BUFFALO L. REV. 313, 323–28 & nn.28–33 (2018) (describing the harms from marijuana use) [hereinafter Larkin, *Gummy Bears*]; Larkin, *Drugged Driving*, *supra* note 36 (describing the harms resulting from marijuana-impaired driving).

54. *See* Aggarwal et al., *supra* note 31, at 162 ("In its 4,000+ years of documented use, there is no report of death from overdose with cannabis. In contrast, as little as 2 grams of dried opium poppy sap can be a lethal dose in humans as a result of severe respiratory depression."); *see also, e.g.*, ASSESSING THE SCIENCE BASE, *supra* note 18, at 6 ("[E]xcept for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications."); Wayne Hall & Louisa Degenhardt, *Adverse Health Effects of Non-Medical Cannabis Use*, 374 LANCET 1383, 1389 (2009) ("The public health burden of cannabis is probably modest compared with that of alcohol, tobacco, and other illicit drugs."). That being said, there is reason to be concerned that marijuana use could prove fatal for some people, such as minors, particularly very young children. Larkin, *Gummy Bears*, *supra* note 53, at 383 n.30 ("Recently, an eleven-month old infant died from what physicians surmised (because no other cause was found) was marijuana-induced myocarditis (inflammation of the heart muscle."); *see* Thomas M. Nappe & Christopher O. Hoyte, *Pediatric Death Due to Myocarditis After Exposure to Cannabis*, 1 CLINICAL PRAC. & CASES EMERGENCY MED. 166 (2017) (describing incident); Matthew J. Noble et al., *Acute Cannabis Toxicity*, 24 CLIN. TOXICOLOGY 1 (2019) (noting that, in a five-month observational study of poison center information in Alaska and Oregon, eight subjects were admitted to an intensive care unit, including three patients who were intubated, with one subject dying, and that children had a higher likelihood of intensive care unit admission and intubation following exposure to concentrated marijuana products).

### *D. Smokable Cannabis Is an Efficient THC-Delivery System*

People can use cannabis in alternative ways. Some prefer marijuana edibles; others use ointments with THC. Smoking marijuana, however, delivers its potential analgesic effect to the brain very quickly. Some of the effect is felt in seconds, with the full effect in minutes. By contrast, ingesting marijuana can take one or more hours to have an effect and requires two or three times as much THC due to metabolism of the edible item.[55] It makes sense, therefore, to allow chronic pain suffers to smoke marijuana to receive pain relief efficiently.

### *E. Scientific Evidence Has Proved that Smokable Cannabis Has Analgesic Benefits*

Advocates for using cannabis as a long-term analgesic also rely on two types of evidentiary support. The first one consists of anecdotal stories and survey responses by individuals for whom cannabis provides pain relief unavailable through other non-opioid drugs.[56] That has been the traditional means of defending cannabis's analgesic efficacy.[57] The second basis is a series of scientific reports indicating either that patients in clinical trials report cannabis's analgesic efficacy[58] or studies reporting a reduction in the number of opioid prescriptions in states that have medical marijuana programs.[59] But perhaps the strongest basis

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55. *See* BRICK & ERICKSON, *supra* note 21, at 106; IVERSEN, *supra* note 31, at 41–47, 129; Larkin *Gummy Bears*, *supra* note 53, at 320.

56. *See, e.g.*, LESTER GRINSPOON & JAMES B. BAKALAR, MARIJUANA: THE FORBIDDEN MEDICINE 109–23 (rev. ed. 1997) (discussing personal accounts of marijuana-provided chronic pain relief); Boehnke et al., *supra* note 20 (results from an online questionnaire showed that 64% of respondents' using medical cannabis decreased their opioid use and 45% reported a better quality of life); Mark A. Ware at al., *Cannabis Use for Chronic Non-Cancer Pain: Results of a Prospective Survey*, 102 PAIN 211, 214 (2003) (discussing survey of patients at a pain management unit: "This survey found that cannabis use among chronic pain patients is not uncommon. Ten percent of the population studied was currently using cannabis for pain relief and another 5% had tried cannabis for pain relief.").

57. *See* Fiona A. Campbell et al., *Are Cannabinoids an Effective and Safe Treatment in the Management of Pain? A Qualitative Systematic Review*, 323 BRITISH MED'L J. 1, 1 (2001) ("The evidence used in the public debate about the analgesic efficacy of cannabinoids in humans has been gathered in a less than systematic manner and has often been taken from low quality study designs, such as anecdotal reports, questionnaires, or case series.").

58. *See, e.g.*, Mark A. Ware et al., *Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial*, 182 CAN. MED. ASS'N J. e694 (2010). Not every study indicating that marijuana is a useful treatment for chronic pain, however, used smoked cannabis or has the same persuasive value. *See* Whiting et al., *supra* note 33, at 2457 ("Chronic pain was assessed in 28 studies. Thirteen studies evaluated nabiximols, 4 were for smoked THC, 5 for nabilone, 3 for THC oromucosal spray, 2 dronabinol, 1 vaporized cannabis (including 2 doses), 1 for ajuvenic acid capsules, and 1 for oral THC. . . . Two studies were at low risk of bias, 9 at unclear risk, and 17 at high risk.").

59. *See, e.g.*, Terrance Bellnier et al., *Preliminary Evaluation of the Efficacy, Safety, and Costs Associated with the Treatment of Chronic Pain with Medical Cannabis*, 8 MENTAL HEALTH CLINICIAN 110 (2018); Ashley C. Bradford et al., *Association between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population*, 178 JAMA INTERNAL MED. 667 (2018); Ashley C. Bradford & W. David Bradford, *Medical Marijuana Laws May be Associated with a Decline in the Number of Prescriptions for Medicaid Enrollees*, 36 HEALTH AFFAIRS 945 (2017); Ashley C. Bradford & W. David Bradford, *Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D*,

are two studies within the last four years—one in 2014, the other in 2017—that compared the number of opioid-related fatal overdoses in states with and without laws authorizing the medical use of marijuana.[60] The studies found that a fatal opioid overdose rate of 25–40% less in the former than in the latter. That conclusion makes sense, they argued, because cannabinoids receptors in the brain can block pain signals.[61]

* * * * *

In sum, advocates for cannabis advance the view that, because it poses far fewer and far less severe risks than long-term use of opioids, it makes sense, from both a patient-oriented and public-health perspective, to allow physicians to recommend use of cannabis when, in their best professional judgment, their patients would benefit from its use.

## IV. THE PROBLEMS WITH RESORTING TO MARIJUANA AS AN ANALGESIC

It may well be that most of the advocates supporting cannabis as a long-term treatment for chronic pain are motivated entirely by a desire to relieve the suffering of the afflicted while benefitting society as well.[62] Some marijuana advocates focus on the inadequate relief of current approaches for pain management in individuals harboring a number of debilitating chronic diseases or symptoms, including Multiple Sclerosis, Crohn's disease, Alzheimer's disease, cancer, and chronic pain.

For a number of reasons, however, marijuana is unlikely to be the answer to today's opioid overdose problem.[63] As explained below, the studies performed to

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35 HEALTH AFFAIRS 1230 (2016); Hefei Wen & Jason M. Hockenberry, *Association of Medical and Adult-Use Marijuana Laws with Opioid Prescribing for Medicaid Enrollees*, 178 JAMA INTERNAL MED. 673 (2018).

60. *See* Marcus A. Bachluber et al., *Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States*, 1999–2010, 174 JAMA INTERNAL MED. 1668 (2014); Powell et al., *supra* note 8.

61. *See* Bachluber, *supra* note 60, at 1672.

62. At the same time, not everyone advocating that position has done so in good faith. *See* Larkin, *Drugged Driving*, *supra* note 36, at 512 ("[A] large segment of the nation's population justifiably believes that the medical marijuana movement is merely a Trojan horse for legalization. To them, the sponsors of those initiatives took advantage of the natural sympathy that people have for others in extremis to achieve dishonestly what could not be done openly: legalize marijuana use."); Budney et al., *supra* note 31, at 233 ("The argument that cannabis has legitimate medical benefits has also been used to support the call for legalization and decriminalization, but one must recognize that 'medical potential' could be claimed for most other substances that are abused and currently illegal."). That is particularly true given the fortune that some people hope to make from selling marijuana. *See* Larkin, *Gummy Bears*, *supra* note 53, at 355 ("Estimates are that marijuana legalization will generate thousands of jobs, along with billions of dollars in revenues for private parties and state governments over the next few years."). Marijuana's supporters are not all benevolent humanitarians.

63. *See, e.g.*, John W. Finney et al., *What Ecologic Analysis Cannot Tell Us About Medical Marijuana Legalization and Opioid Pain Medication Mortality*, 175 JAMA INTERNAL MED. 655 (2015); Hall et al., *supra* note 15; Saxon & Browne, *supra* note 15, at 5.

date do not support the conclusion that we should rely on marijuana to solve our opioid overdose epidemic. Instead, growing evidence is supportive of the opposite conclusion. At best, specific cannabinoids might be a useful adjunctive therapy, such as the synthetic form of THC (Dronabinol) that the FDA approved in 1985 for chemotherapy-induced nausea, vomiting, and appetite enhancement. Nonetheless, Nabiximols—a cannabis extract containing THC and cannabidiol—failed to demonstrate efficacy in Phase 3 clinical trials for cancer pain.[64] Smoking marijuana is not a substitute for using a prescription or over-the-counter painkiller, or alternative means for pain reduction.

### *A. The Limitations of Smokable Cannabis as a Medicine*

A threshold requirement is to define the relevant items of concern. Marijuana acquired its fame or notoriety when people smoked it in the 1960s as a symbol of youthful exploration or protest. Since then, people use it principally as a means of obtaining a euphoric feeling. Smoking botanical marijuana currently marketed in dispensaries or on the street, however, gives rise to a variety of problems—such as dosage, purity, THC and CBD concentration, and so forth—when attempting to measure the usefulness of marijuana as an analgesic (or for some other therapeutic purpose).

To start, there are several reasons why there is no standard terminology for marijuana and no standard "dosage" when marijuana is taken in that manner. Medications distributed in pill form, for example, come with a specified dosage of an active ingredient measured in milligrams. The directions for its use, which must be part of the label, state how many pills should be taken and how frequently. There is currently no comparable uniform measurement or standard for the amount of marijuana's components that a person inhales when smoking or vaping cannabis. There is no standard number of inhalations, no standard depth

64. *Cannabis and Cannabinoids (PDQ)–Health Professional Version*, NAT'L CANCER INST. (Jan. 17, 2019), https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq [https://perma.cc/7S85-XBRV] ("Dronabinol, a synthetically produced delta-9-THC, was approved in the United States in 1986 as an antiemetic to be used in cancer chemotherapy."); *see Researching the Potential Medical Benefits and Risks of Marijuana: Hearing Before the Subcomm. on Crime & Terrorism, S. Comm. on the Judiciary*, 114th Cong. (2016), https://www.fda.gov/NewsEvents/Testimony/ucm511057.htm (statement of Douglas C. Throckmorton, M.D., Deputy Dir. for Regulatory Programs, Ctr. for Drug Evaluation and Research, Food and Drug Admin.) ("Through the drug development processes described above, FDA has approved three drugs for human use which contain active ingredients that are present or similar to those present in botanical marijuana. FDA approved Marinol Capsules in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who had failed to respond adequately to conventional antiemetic treatments. Marinol Capsules include the active ingredient dronabinol, a synthetic delta-9-tetrahydrocannabinol, or THC, which is a psychoactive component of marijuana. Marinol Capsules were approved in 1992 for the treatment of anorexia associated with weight loss in patients with AIDS. FDA recently approved Syndros, a dronabinol oral solution, for the same indications as Marinol. FDA approved Cesamet Capsules for the treatment of nausea and vomiting associated with chemotherapy in 1985. Cesamet Capsules contain the synthetic cannabinoid nabilone as the active ingredient.").

of each inhalation, and no standard length of inhalations.[65] Even if smoking combustible marijuana enabled someone to capture the therapeutic benefits of one or more cannabinoids, a physician would not be able to know precisely how much of those constituents the individual received.

In fact, marijuana users ordinarily titrate the amount they inhale to achieve a particular degree of euphoria without succumbing to the adverse short-term consequences that can follow from over-using cannabis (e.g., hallucinations).[66] As the ironic result, marijuana is consumed in a manner that is in direct opposition to the methods devised and generally used over the last eighty years to regulate the safety and effectiveness of medications (since the Federal Food, Drug, and Cosmetic Act became law in 1938). Perhaps that is why there is no FDA-approved medicine that is smoked.[67] As the Surgeon General of the United States put it in 2016, "Evidence collected so far in clinical investigations of the marijuana plant is still insufficient to meet FDA's standards for a finding of safety and efficacy for any therapeutic indications."[68]

It also is practically impossible for a physician to know precisely what amount of THC could be delivered to a patient by smoking marijuana, because marijuana is not a uniform commodity or a "standardized good."[69] Ordinary prescription and over-the-counter medications have standard formulations, potency, and a known range of pharmacokinetics and pharmacodynamics; marijuana does not. Marijuana is not at all a homogeneous product. Its potency can vary according to factors such as strain, breeding, the region where it is grown, its manner of cultivation, storage time, and the way that it is used.[70] Consider the enormous difference between the amount of THC contained in marijuana when it was symbol of protest half a century ago and when it is used as an intoxicant today. The THC content of the plant form of marijuana consumed in the 1960s through the 1980s was approximately 1–3%. Today, that number can be between 12 and 20% in the

65. *See* MEYER & QUENZER, *supra* note 19, at 404 ("In practice, the amount of THC absorbed is affected not only by the initial amount of plant materials used and the potency of this material, but also by the pattern of smoking. The effective dose and latency to onset of effects of smoked marijuana are influenced by puff volume, puff frequency, inhalation depth, and breath-hold duration. . . ."); Ashton, *supra* note 53, at 638 ("The amount absorbed through the lungs depends on smoking style. In experienced smokers, who inhale deeply and hold the smoke in the lungs for some seconds before exhaling, virtually all of the cannabinoids present in the mainstream smoke enter the bloodstream."); Paul J. Larkin, Jr., *The Medical Marijuana Delusion*, U. PENN. REG. REV. (Dec. 17, 2018), https://www.theregreview.org/2018/12/17/larkin-medical-marijuana-delusion/ [https://perma.cc/QL57-XSST]; Saxon & Browne, *supra* note 15, at 4. SyqE, a company based in Israel, however, claims to have invented a device that gives a metered dose of inhaled marijuana. *See* SYQE MEDICAL, http://www.syqemedical.com/ (last visited May 23, 2019). The device, however, has not yet been approved for sale in the United States.

66. *See* Bostwick, *supra* note 51, at 2–3. Other adverse effects are cognitive and psychomotor impairment, anxiety, panic attacks, paranoia, acute psychosis, blurred vision, heart palpitations, tachycardia, postural hypotension (viz., fainting), and xerostomia ("cotton mouth"). Ashton, *supra* note 53, at 639–44; Campbell et al., *supra* note 57, at 1.

67. *See* Compton et al., *supra* note 34, at 560.

68. OFFICE OF THE SURGEON GEN., *supra* note 43, at 1-21 to 1-22.

69. CAULKINS ET AL., MARIJUANA LEGALIZATION, *supra* note 18, at 34.

70. *See, e.g.*, *id.* at 68.

plant form or in hashish (dried cannabis resin and crushed plants), with hash oil (an oil-based extract of hashish) having an even greater THC content and range: 15–50%.[71] As some experts put it, "asking about, or trying to study, the benefits (or harms) of marijuana generically is a little bit like asking what wine tastes like, as if merlot and champagne were interchangeable."[72]

Marijuana is also not subject to the same manufacturing and processing safety protocols that pharmaceutical companies must follow when mass-producing an FDA-approved drug.[73] Commercial marijuana—such as what is available in stores or dispensaries in Colorado and in other states that have medical or recreational marijuana laws—lacks the purity and consistency of ordinary commercial pharmaceuticals. In the words of Dr. Robert DuPont, former head of the National Institute on Drug Abuse, marijuana "is not a single specific chemical"; it is "a complex chemical slush."[74] Atop that, various chemicals, pesticides, fungi, mold, lead, formaldehyde, and other substances can and have contaminated commercial

71. *See, e.g.*, BRICK & ERICKSON, *supra* note 21, at 105; Budney et al., *supra* note 31, at 216 (the potency of marijuana increased by 60% over 2000–2010); Suman Chandras et al., *New Trends in Cannabis Potency in USA and Europe During the Last Decade (2008–2017)*, 269 EUR. ARCHIVES PSYCHIATRY CLINICAL NEUROSCIENCE 5 (2019) ("[T]he mean Δ9-THC concentration has increased dramatically over the last 10 years, from 8.9% in 2008 to 17.1% in 2017. The mean Δ9-THC:CBD ratio also rose substantially from 23 in 2008 to 104 in 2017. There was also marked increase in the proportion of hash oil samples (concentrates) seized (0.5–4.7%) and their mean Δ9-THC concentration (6.7–55.7%) from 2008 to 2017."); Compton et al., *supra* note 34, at 559 (noting that "[i]n recent years, the potency of cannabis [THC content] . . . has increased 3-fold to 4 fold"); ROOM ET AL., *supra* note 18, at 6 (noting that some varieties of marijuana like Sinsemilla, also known as skunk and Netherweed, may have THC content as high as 20%, that hashish has a THC content in the range of 2–20%, and that hash oil has a THC content of 15–50%); Wayne Hall & Louisa Degenhardt, *High Potency Cannabis: A Risk Factor for Dependence, Poor Psychosocial Outcomes, and Psychosis*, 350 BRITISH MED. J. 1205 (2015); Eric L. Sevigny et al., *The Effects of Medical Marijuana Laws on Potency*, 25 INT'L J. DRUG POL'Y 308, 309 (2014) ("Although direct empirical evidence is limited, insider and journalistic accounts suggest that [medical marijuana laws—and the medical marijuana industry built up around them—have greatly enhanced the development and diffusion of high-potency cannabis cultivars and sophisticated techniques of production."); Volkow et al., *supra* note 53, at 2222 ("The THC content, or potency, of marijuana, as detected in confiscated samples, has been steadily increasing from about 3% in the 1980s to 12% in 2012. . . . This increase in THC content raises concerns that the consequences of marijuana use may be worse now than in the past and may account for the significant increases in emergency department visits by persons reporting marijuana use . . . and the increases in fatal motor-vehicle accidents."). THC doses in FDA-approved Marinol (near 100% THC but the final starting oral dose is 2.5 mg) are far lower than THC found in marijuana dispensaries (20% THC or ∼64 mg THC delivered more efficiently by smoking directly). The limiting factor is benefit:cost or therapeutic:intoxicant THC levels combined with their therapeutic efficacy. For example, nabiximols (THC combined with CBD) failed two objective randomized controlled Phase 3 clinical trials in the United States, for various levels of cancer pain.

72. CAULKINS ET AL., MARIJUANA LEGALIZATION, *supra* note 18, at 68; *see also* Larkin, DuPont & Madras, *supra* note 19, at 8–9 n.25 (collecting authorities); Larkin *Gummy Bears*, supra note 53, at 346 n.81.

73. The Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified, as amended, at 21 U.S.C. Ch. 9), prohibits the distribution in interstate commerce of "adulterated" or "misbranded" food and drugs as well as "new drugs" that have not yet been approved for distribution by the FDA. *See, e.g.*, 21 U.S.C. §§ 331(a), 332–337a, 342–43, 351–52, 355 (2012).

74. ROBERT L. DUPONT, THE SELFISH BRAIN: LEARNING FROM ADDICTION 142 (1997).

marijuana.[75] Those substances would render a commercial pharmaceutical unsafe for use and subject to legal action by the FDA.[76]

The demands imposed by modern medicine and required by federal law are critically important. Until the mid-1900s, there were few chemically pure medicines available to physicians, so it was "common" for them to use "complex natural substances," such as cannabis.[77] The world is quite different today. Today's medicines contain "pure and stable" chemicals, "free of a hodgepodge of inactive and potentially harmful substances," which might contain known inert fillers, but as a regulated pharmaceutical, it enables physicians to know "precisely what their patients are taking."[78] That is not true when someone smokes cannabis. "Marijuana, with over 700 chemicals, let alone marijuana smoke with the production of other chemicals, many of which are known to be harmful to the user's health, is not an attractive modern medicine."[79] The term "medical marijuana" also disregards the complexity of the plant and the fact that different cannabinoids can have adverse or beneficial effects on brain function and even opioid sensitivity.[80]

Consider the two most common cannabinoids in marijuana, THC and cannabidiol. Over the last two decades, THC levels in street marijuana have risen dramatically, while cannabidiol (CBD) levels have declined, yielding increasing ratios

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75. *See, e.g.*, Franziska Busse et al., *Lead Poisoning Due to Adulterated Marijuana*, 358 NEW ENGLAND J. MED. 1641 (2008); Tista Ghosh et al., *The Public Health Framework of Legalized Marijuana in Colorado*, 106 AM. J. PUB. HEALTH 21, 23 (2016) ("The medical literature reports that marijuana can be contaminated by bacteria, mold, chemicals such as pesticides, lead, ammonia, and formaldehyde.") (footnotes omitted); Camille Gourdet et al., *How Four U.S. States Are Regulating Recreational Marijuana Edibles*, 43 INT'L J. DRUG POL'Y 83, 88 (2017); Larkin, *Gummy Bears*, *supra* note 53, at 346 n.81 ("Various reports have also indicated that, despite efforts to avoid contamination, marijuana sold in states such as Colorado and California have been found to contain bacteria, mold, fungi, pesticides, heavy metals, and solvents such as butane and propane."); Todd Subritzky et al., *Issues in the Implementation and Evolution of the Commercial Recreational Cannabis Market in Colorado*, 27 INT'L J. DRUG POL'Y 1, 6 (2016) ("the presence of fungus and residues remains problematic in Colorado").

76. *See* Larkin, *Gummy Bears*, *supra* note 53, at 344–49.

77. DUPONT, *supra* note 74, at 148.

78. *Id.*

79. *Id.*

80. For example, studies using rodents showed that exposure to THC during adolescence increased the likelihood of greater opioid use. *See* Christina Cadoni et al., *Strain Dependence of Adolescent Cannabis Influence on Heroin Reward and Mesolimbic Dopamine Transmission in Adult Lewis and Fischer 344 Rats*, 20 ADDICTION BIOLOGY 132 (2015); Marie Ellgren et al., *Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Populations in Adult Rats*, 32 NEUROPSYCHOPHARMACOLOGY 607 (2007); Serena Stopponi et al., *Chronic THC During Adolescence Increases the Vulnerability to Stress-Induced Relapse to Heroin Seeking in Adult Rats*, 24 EUR. NEUROPSYCHOPHARMACOLOGY 1037 (2014); Hilarie C. Tomasiewicz et al., *Proenkephalin Mediates the Enduring Effects of Adolescent Cannabis Exposure Associated with Adult Opiate Vulnerability*, 72 BIOLOGICAL PSYCHIATRY 803 (2012). Those studies raise the question whether heavy marijuana use during human adolescence poses the risk of greater opioid dependence during adulthood. Since no one has yet figured out a way to prevent minors from using marijuana, encouraging adults to smoke marijuana as an analgesic is likely to worsen the long-term risks of opioid abuse.

of THC:CBD as high as 80:1.[81] In the current unregulated market, marijuana's THC:CBD ratios vary from 2:1 to 80:1 or even higher. The changing THC:CBD ratio is quite important for public health purposes. THC and CBD produce different, or possibly antagonistic molecular, neuropsychiatric, and pharmacological effects.[82] The pharmacological effects that limit the therapeutic potential of THC in marijuana are addiction, anxiety, intoxication, impairment of cognition, amotivational syndrome, and psychosis. CBD not only has a wide safety margin, but also no evidence has emerged that it is addictive, produces euphoria or intoxication, or impairs cognition or precipitates psychosis.[83] But with accumulating evidence, it is clear that CBD is not pharmacologically silent. High THC:CBD ratios in marijuana are associated with heightened euphoria, anxiety, and psychotic symptoms, whereas low THC:CBD ratios are linked to sedation and attenuation of THC-induced psychosis, anxiety, and cognitive deficits, leading to the conclusion, that CBD dampens the adverse effects of THC.[84]

THC and CBD also have different effects on the pharmacodynamics of opioids.[85] For example, we cannot yet say that CBD will reduce or eliminate all adverse effects of THC,[86] but preliminary data indicate that CBD does attenuate specific THC-elicited neuroadaptations.[87] Given that data, we might soon find

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81. *See* Mahmoud A. ElSohly et al., *Changes in Cannabis Potency over the Last 2 Decades (1995–2014): Analysis of Current Data in the United States*, 79 BIOLOGICAL PSYCHIATRY 613 (2016).

82. *See* Amir Englund et al., *Can We Make Cannabis Safer?*, 4 LANCET PSYCHIATRY 643 (2017).

83. *See* Shanna Babalonis et al., *Oral Cannabidiol Does Not Produce a Signal for Abuse Liability in Frequent Marijuana Smokers*, 172 DRUG & ALCOHOL DEPENDENCE 9 (2017); Margaret Haney et al., *Oral Cannabidiol Does Not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis*, 41 NEUROPSYCHOPHARMACOLOGY 1974 (2016); Alex F. Manini et al., *Safety and Pharmacokinetics of Oral Cannabidiol When Administered Concomitantly with Intravenous Fentanyl in Humans*, 9 J. ADDICTION MED. 204 (2015); Philip McGuire et al., *Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial*, 175 AM. J. PSYCHIATRY 225 (2018); Kerstin Iffland & Franjo Grotenhermen, *An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies*, 2 CANNABIS & CANNABINOID RES. 139 (2017).

84. *See* Christian D. Schubart et al., *Cannabis with High Cannabidiol Content Is Associated with Fewer Psychotic Experiences*, 130 SCHIZOPHRENIA RESEARCH 216 (2011).

85. In preclinical research on rodents, THC enhances reward sensitivity to opioids, whereas CBD reduces morphine reward and cue-induced heroin-seeking behavior. *See* Stopponi et al., *supra* note 80; Cadoni et al., *supra* note 80; Tomasiewicz et al., *supra* note 80; Ellgren et al., *supra* note 80; Vicky Katsidoni et al., *Cannabidiol Inhibits the Reward-Facilitating Effect of Morphine: Involvement of 5-HT1A Receptors in the Dorsal Raphe Nucleus*, 18 ADDICTION BIOLOGY 286 (2013); Yanhua Ren et al., *Cannabidiol, a Nonpsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances*, 29 J. NEUROSCIENCE 14764 (2009). These preclinical data have catalyzed research on the therapeutic potential of CBD for treating opioid use disorder and other substance use disorders. *See, e.g.*, Yasmin L. Hurd et al., *Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage*, 12 NEUROTHERAPEUTICS 807 (2015).

86. See Douglas L. Boggs et al., *Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ(9)-Tetrahydrocannabinol*, 43 NEUROPSYCHOPHARMACOLOGY 142 (2018).

87. *See* Bertha K. Madras et al., *Dramatic Increase of Dopamine D1–D2 Receptor Heteromers by Tetrahydrocannabinol (THC) in Primate Caudate Nucleus is Attenuated by Cannabidiol (CBD)*, NEUROPSYCHOPHARMACOLOGY (2016), https://acnp.org/videos/bertha-madras/ [https://perma.cc/RL84-AGVB].

that CBD is not only useful for the treatment of childhood forms of epilepsy, as the FDA concluded in 2018, but also is helpful in treating opioid abuse. Ironically, however, the current strains of marijuana sold in states that have liberalized their cannabis laws often have a low level of CBD.

That is a critical but largely undiscussed or under-discussed fact in the current debate. Unless designed specifically to enrich the plant with cannabidiol, the marijuana industry has essentially bred cannabidiol out of street marijuana, demonstrating the pitfalls of an unregulated industry operating without an informed scientific basis. Also missing from a rational discussion of using marijuana to treat pain is consideration of the complexity of the spectrum of patients in pain and their likelihood of abusing painkillers. Those facts must be considered in any serious debate over liberalizing marijuana use for medical purposes.

In addition, "the elephant in the room" resides with the psychoactive properties of marijuana. Unlike the vast majority of drugs approved by the FDA, marijuana is an intoxicant within the dose range that is generally marketed as a therapeutic in marijuana dispensaries. Although some measure of tolerance to the intoxicating effects has been reported, the intoxicating effects persist with renewed dosing, which interferes with cognitive function.[88] The window for therapeutic doses and side effects (intoxication, cognitive impairment, coordination, psychosis) overlap extensively. Although the short half-life of marijuana requires frequent dosing during the day to alleviate pain, marijuana advocates rarely acknowledge the impact of cognitive impairment on daily functioning.

Atop that are several other considerations. The effect that THC has on someone varies according to his "set" (viz., user expectation) and the "setting" (viz., environment) in which use occurs.[89] Recruiting marijuana-naïve subjects for clinical trials is risky, as high dropout rates are common. Thus, for example, the vast majority of subjects in Center for Medicinal Cannabis Research-sponsored clinical trials with marijuana for neuropathic pain were experienced marijuana users.[90] Moreover, a long-term marijuana user develops a tolerance to its psychoactive effect, which means that, whatever form of cannabis he uses, he must consume a greater amount of THC than a novice in order to achieve the same euphoric effect. Finally, the process of inhaling marijuana smoke causes a number of adverse health effects, such as bronchitis, tracheal irritation, and, potentially, more serious lung disease.[91] In fact, the nation's consensus that people should not

88. *See* Joao P. De Aquino et al., *The Psychiatric Consequences of Cannabinoids*, CLINICAL THERAPY (2018); Samantha J. Broyd et al., *Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review*, 79 BIOLOGICAL PSYCHIATRY 557 (2016); Johannes G. Ramaekers et al., *Cannabis and Tolerance: Acute Drug Impairment as a Function of Cannabis Use History*, 6 SCI. REP. 26843 (2016) (*Erratum*, 6 SCI. REP. 31939 (2016)).

89. *See* JOHN KAPLAN, MARIJUANA: THE NEW PROHIBITION 56–57 (1969); MEYER & QUENZER, *supra* note 19, at 414.

90. *See* Wilsey et al., *supra* note 50.

91. *See, e.g.*, DUPONT, *supra* note 74, at 143 ("Once the marijuana is smoked, users inhale more than 2,000 different chemicals into their lungs to be taken in their bloodstreams to all of the cells in their bodies."), 144 ("Marijuana smoke contains more tar and cancer-causing chemicals than even cigarette

smoke cigarettes, along with its commitment to the anti-smoking cause[92] because of smoking's irrefutably proven health risks, stands in stark contrast to the nascent effort to persuade legislatures to permit marijuana smoking.

The bottom line is this: The plant form of marijuana possesses neither the qualities and features that the FDA requires for approval of a pharmaceutical as being safe and effective within a specific dose range, nor the features that physicians consider when deciding whether and how much of a drug to prescribe for a patient and assume are present in manufactured pharmaceuticals. That is why, as one observer put it, even putting aside any political and legal considerations, "it remains extremely unlikely that crude cannabis could ever be approved by the FDA as a prescription medicine" in accordance with FDA guidelines.[93]

### *B. The Problems with Using Cannabis as an Analgesic for Acute Pain*

Opioids are markedly effective in providing relief from the agony of surgery, gunshot wounds, cancer, a serious motor vehicle accident, and similar causes of severe acute or long term debilitating pain.[94] Cannabis lacks the potency necessary to provide relief from the acute pain resulting from these events.[95]

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smoke. One marijuana cigarette has as much cancer-causing tar as seventeen tobacco cigarettes. Marijuana smoke, like tobacco smoke, causes bronchitis, inflammation of the airways in the lungs, and chronic respiratory illnesses."); GEORGE F. KOOB ET AL., DRUGS, ADDICTION, AND THE BRAIN 306 (2014) ("Marijuana smoke may also have the same potential toxicity as cigarette smoke with regard to lung function."); Budney et al., *supra* note 31, at 228–29; David Moir et al., *A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions*, 21 CHEMICAL RESEARCH TOXICOLOGY 494 (2008); Volkow et al., *supra* note 53. Marijuana can also be vaporized and inhaled or consumed like food via marijuana edibles, and those mechanisms, while not perfect, do not pose the same health risks as smoking combustible marijuana. *See* Bostwick, *supra* note 51, at 3. Those mechanisms, however, do not eliminate the purity and consistency problems noted above from the use of privately grown marijuana.

92. *See, e.g.*, DAVID KESSLER, WITHOUT INTENT: A GREAT AMERICAN BATTLE WITH A DEADLY INDUSTRY (rev. ed. 2002).

93. Ethan B. Russo, *Cannabinoids in the Management of Difficult to Treat Pain*, 4 THERAPEUTICS & CLINICAL RISK MGMT. 245, 248–50 (2008).

94. *See* MEYER & QUENZER, *supra* note 19, at 305–06 ("As a class, [opioids] are the very best painkillers known to man.").

95. *See, e.g.*, Abhiram R. Bhashyam et al., *Self-Reported Marijuana Use Is Associated with Increased Use of Prescription Opioids Following Traumatic Musculoskeletal Injury*, 100 J. BONE & JOINT SURGERY 2095, 2096 (2018) ("Prior research provided moderate evidence supporting marijuana use for chronic pain. However, the current literature is inadequate to draw meaningful conclusions as to the effectiveness of marijuana as an acute pain reliever."); Campbell et al., *supra* note 57, at 16 ("We found insufficient evidence to support the introduction of cannabinoids into widespread clinical practice for pain management—although the absence of evidence of effect is not the same as the evidence of absence of effect. . . . Cannabis is clearly unlikely to usurp existing effective treatments for postoperative pain."); Noyes et al., *Analgesic Effect of THC*, *supra* note 50, at 139 ("Crude preparations of cannabis sativa were recommended for a variety of painful conditions toward the end of the 19th century. . . . Yet, they proved no match for the potent and rapid acting narcotics and eventually lost favor because their effects were milder and less predictable."); Wilsey, *supra* note 50, at 146 ("[T]he analgesic effect of cannabis in treating acute pain would be less than optimal; this is consistent with the recommendation that cannabinoids are not suitable for postoperative pain."); David Raft et al., *Effects of Intravenous Tetrahydrocannabinol on Experimental and Surgical Pain*, 21 CLINICAL PHARMACOLOGY & THERAPEUTICS 26 (1976).

Advocates for the analgesic use of cannabis, however, maintain that it can be used to address chronic non-cancer pain, but smoking marijuana does not provide sufficient analgesia for people suffering from even those afflictions.

### *C. The Problems with Using Cannabis as an Analgesic for Chronic Pain*

There are four reasons to doubt claims that permitting marijuana use for chronic pain can alleviate the opioid crisis. First, there is insufficient evidence to support the claim that marijuana is a safe and effective analgesic for chronic pain. Second, states with liberal marijuana laws should have seen a decline in opioid overdose deaths, but that has not been the case. Third, individuals using marijuana for pain relief should have shown a reduction of or stoppage in opioid use, but evidence indicates that they have continued to use or even increased opioid use. And fourth, the concomitant use of marijuana and opioids conceivably interferes with treatment for opioid use disorder.[96]

#### 1. There Is Insufficient Evidence that Marijuana Is a Safe and Effective Analgesic

Only a handful of controlled trials of individuals suffering from with neuropathic pain have shown pain reduction using smoked marijuana.[97] Results from those studies are inadequate to recommend long-term use of marijuana, for several reasons. The research was conducted over a very short time (days to weeks); the majority of subjects were experienced marijuana users who were also using prescribed but unreported quantities of opioids; and there is no indication that subjects who were using various prescribed opioids were randomized according to dose, type, and frequency. Moreover, the researchers who conducted the tests did not rigorously ask the test subjects about quality-of-life issues, such as their coping skills and objective measures of daily cognitive functioning.[98] Although the therapeutic efficacy of cannabinoids in reducing chronic pain certainly merits further study, meta-analysis of placebo-controlled studies of the use of whole-plant cannabis or cannabinoids for pain did not find a proven pain-killing effect,

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96. There is also ample reason to be concerned that legitimizing marijuana use would place children at risk. *See* Larkin, *Gummy Bears*, *supra* note 53.

97. *See* Mark S. Wallace et al., *Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy*, 16 J. PAIN 616 (2015); Ware et al., *supra* note 56, at E694; Donald I. Abrams et al., *Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial*, 68 NEUROLOGY 515 (2007); Barth Wilsey et al., *A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain*, 9 J. PAIN 506 (2008); Wilsey et al., *supra* note 50; Ronald J. Ellis et al., *Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial*, 34 NEUROPSYCHOPHARMACOLOGY 672 (2009).

98. *See, e.g.*, Keith Humphreys & Richard Saitz, *Should Physicians Recommend Replacing Opioids with Cannabis?*, 321 JAMA 639, 639 (2019) ("There are no randomized clinical trials of substituting cannabinoids for opioids in patients taking or misusing opioids for treatment of pain, or in patients with opioid addiction treated with methadone or buprenorphine. . . . Many factors other than cannabis may affect opioid overdose deaths, such as prescribing guidelines, opioid rescheduling, Good Samaritan laws, incarceration practices, and availability of evidence-based opioid use disorder treatment and naloxone.").

and any overall effect for alleviating pain was not statistically significant.[99] Atop that, there is stronger evidence supporting the effectiveness of nonpharmacological therapies, such as exercise, rehabilitation, acupuncture, and non-psychoactive, non-steroidal, anti-inflammatory medications for the treatment of lower back pain, the leading cause of disability worldwide, than for use of plant marijuana as a treatment.[100] As Dr. Mark Olfson, a Columbia University professor of psychiatry and epidemiology, has concluded:

> Overinterpreting results from ecological studies linking medical marijuana legislation to declining opioid mortality temporarily requires caution. Much remains to be learned about the complex relationships between cannabis and opioid use and how these interactions vary by patient characteristics and cannabinoid formulation. In the absence of prospective clinical evidence demonstrating protective effects, however, there is currently little medical justification for authorizing medical cannabis to lower nonmedical opioid use.[101]

That conclusion is consistent with a 2017 overview coordinated by the Department of Veterans Affairs (DVA). The DVA report—*Benefits and Harms of Cannabis in Chronic Pain or Post-Traumatic Stress Disorder*—summarized its conclusion as follows:

> In 27 chronic pain trials, there is low-strength evidence that cannabis preparations with precisely defined THC:CBD content (most in a 1:1 to 2:1 ratio) have the potential to improve neuropathic pain but insufficient evidence in other pain patient populations. Most studies are small, many have methodologic[al] flaws, and the long-term effects are unclear given the brief follow-up duration of most studies. The applicability of these findings to current practice may be low in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain.[102]

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99. *See* Mücke et al., *supra* note 33; Holly T. Philpott et al., *Attenuation of Early Phase Inflammation by Cannabidiol Prevents Pain and Nerve Damage in Rat Osteoarthritis*, 158 PAIN 2442 (2017); Whiting et al., *supra* note 33.

100. *See* Roger Chou et al., *Nonpharmacologic Therapies for Low Back Pain: A Systematic Review of an American College of Physicians Clinical Practice Guideline*, 166 ANNALS INTERNAL MED. 193 (2017); Krebs et al., *supra* note 29.

101. Mark Olfson et al., *Medical Marijuana and the Opioid Epidemic: Response to Theriault and Schlesinger*, 175 AM. J. PSYCHIATRY 284 (2018).

102. KANSAGARA ET AL., *supra* note 15; *see also, e.g.*, Humphreys & Saitz, *supra* note 98 ("Recent systematic reviews identified low-strength evidence that plant-based cannabis preparations alleviate neuropathic pain and insufficient evidence for other types of pain. Studies tend to be of low methodological quality, involve small samples and short-follow-up periods, and do not address the most common causes of pain ([e.g.,] back pain). This description of evidence for efficacy of cannabis for chronic pain is similar to how efficacy studies of opioids for chronic pain have been described (except that the volume of evidence is greater for opioids with 96 trials identified in a recent systematic

According to eleven systematic reviews and thirty-two primary studies, marijuana-use harms include increased risk for motor vehicle accidents, psychotic symptoms, amotivational syndrome, and short-term cognitive impairment.[103] There are few methodologically rigorous trials; the types of cannabis studied may not reflect commercially available products and are of limited applicability to older, chronically ill populations as well as patients who use cannabis heavily. Finally, although there was no evidence of adverse pulmonary effects in younger populations, there was evidence of long-term physical harms in older populations and in heavy or long-term cannabis users.[104]

A recent—and rare—four-year longitudinal cohort study published in the peer-reviewed journal *Lancet Public Health* concludes that cannabis does not provide long-term relief from chronic non-cancer pain.[105] The authors conducted their research for two reasons. One was the scarcity of longitudinal studies of cannabis

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review)."); Nugent et al., *supra* note 33; Shannon M. Nugent & Devan Kansagara, *The Effects of Cannabis Among Adults With Chronic Pain*, 168 ANNALS INTERNAL MED. 525 (2018).

103. *See* SCHIZOPHRENIA COMMISSION, THE ABANDONED ILLNESS: A REPORT BY THE SCHIZOPHRENIA COMMISSION, RETHINK MENTAL ILLNESS (2012); Mohini Ranganathan & Deepak D'Souza, *The Acute Effects of Cannabinoids on Memory in Humans: A Review*, 188 PSYCHOPHARMACOLOGY 425 (2006); Rebecca D. Crean et al., *An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions*. 5 J. ADDICTIVE MED. 1 (2011); Natania A. Crane et al., *Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences*, 23 NEUROPSYCHOLOGY REV. 117 (2013); Mark Asbridge et al., *Acute Cannabis Consumption and Motor Vehicle Collision Risk: Systematic Review of Observational Studies and Meta-Analysis*, 9 BMJ 344 (2012); Nugent et al., *supra* note 33; William H. McGlothlin et al., *The Marihuana Problem: An Overview*, 125 AM. J. PSYCHIATRY 126 (1968); Edmund Silins et al., *Cannabis Cohorts Research Consortium. Young Adult Sequelae of Adolescent Cannabis Use: An Integrative Analysis*, 1 LANCET PSYCHIATRY 286 (2014); Sven Andreasson et al., *Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts*, 2 LANCET 1483 (1987); Louise Arseneault et al., *Cannabis Use in Adolescence and Risk for Adult Psychosis: Longitudinal Prospective Study*, 325 BMJ 1212 (2002); Stanley Zammit et al., *Self-Reported Cannabis Use as a Risk Factor for Schizophrenia in Swedish Conscripts of 1969: Historical Cohort Study*, 325 BMJ 1199 (2002); Deepak Cyril D'Souza et al., *The Psychotomimetic Effects of Intravenous Delta-9-Tetrahydrocannabinol in Healthy Individuals: Implications for Psychosis*. 29 NEUROPSYCHOPHARMACOLOGY 1558 (2004); Jouko Miettunen et al., *Association of Cannabis Use with Prodromal Symptoms of Psychosis in Adolescence*, 192 BRITISH J. PSYCHIATRY 470 (2008); Mathew M. Large et al., *Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-Analysis*. 68 ARCHIVES GEN'L PSYCHIATRY 555 (2011); Mario 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 RESearch 116 (2012); Marta Di Forti et al., *Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users*, 40 SCHIZOPHRENIA BULLETIN 1509 (2014); Marta Di Forti et al., *High-Potency Cannabis and the Risk of Psychosis*, 195 BRITISH J. PSYCHIATRY 488 (2009); Marta Di Forti et al., *Proportion of Patients in South London with First-Episode Psychosis Attributable to Use of High Potency Cannabis: A Case-Control Study*, 2 LANCET PSYCHIATRY 233 (2015); Robin M. Murray et al., *Cannabis-Associated Psychosis: Neural Substrate and Clinical Impact*, 124 NEUROPHARMACOLOGY 89 (2017).

104. *See* Bao et al., *supra* note 33; Harrison et al., *supra* note 33; Koppel et al., *supra* note 33; Mücke et al., *supra* note 33; Nugent et al., *supra* note 33; Salottolo et al., *supra* note 33; Whiting et al., *supra* note 33.

105. Gabrielle Campbell et al., *Effect of Cannabis Used in People with Chronic Non-Cancer Pain Prescribed Opioids: Findings from a 4-year Prospective Cohort Study*, 3 LANCET PUB. HEALTH e341 (2018).

use by people suffering from non-cancer pain.[106] The other was the lack of prior studies that included persons with "complex physical, substance use, and mental health comorbidities," which they saw as a weakness because such individuals "represent a substantial portion of people living with chronic non-cancer pain."[107]

To determine whether marijuana alleviates chronic (viz., longer than three months) non-cancer pain and leads to a reduction or cessation of opioid use, the study investigated the results of 1,500 adults across Australia who had been prescribed opioids.[108] At three- and four-year follow-up interviews, study participants were questioned whether their cannabis use affected their opioid use. The authors found a marked difference between the participants' reported and actual use of the two drugs. On the one hand, the vast majority of participants reported that "cannabis had no effect on their use of opioid medication" (78% at the three-year point; 70% at the four-year point). On the other hand, a minority of participants reported that they sometimes or regularly reduced their opioid medication when using cannabis" (22% at three year; 46% at four).[109] That was so even though the most common reasons cited by participants for their cannabis use was "to relieve pain" and "to offset pain-related distress."[110] What is particularly significant is the finding that participants who used cannabis daily (or less frequently) "reported greater pain severity and pain interference, lower pain self-efficacy, and higher levels of generalized anxiety disorder than those not using cannabis."[111] Moreover, individuals who used marijuana on a near-daily basis were less likely to discontinue morphine use (9%) than participants who did not use cannabis at all (21%), even though there was no material difference between the groups regarding the amount of morphine they consumed.[112]

The authors distinguished earlier cross-sectional studies suggesting that "cannabis might have opioid-sparing effects in people with chronic non-cancer pain," on the ground that there was "a lack of high-quality clinical studies testing potential opioid-sparing effects."[113] Nonetheless, they concluded that their approach

106. *Id*.

107. *Id*. at e342 (footnote omitted).

108. "We aimed to investigate the following: cannabis use during a four-year period in which people with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use in the past month and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time, controlling for potential confounding of demographic and clinical variables; and potential opioid-sparing effects of cannabis, controlling for potential confounding variables." *Id*. Some of the original cohort did not complete the four-year study. *Id*. at e345.

109. *Id*. at e346.

110. *Id*.

111. *Id*. at e347 & tbl. 2.

112. *Id*. at e347. Cannabis use before participating in the study was not independently associated with current pain interference. *Id*.

113. *Id*. (citing Suzanne Nielsen et al., *Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis*, 42 NEUROPSYCHOPHARMACOLOGY 1752 (2017)). The 2017 Nielsen study found a significant difference between pre-clinical and clinical studies of the palliative adjunctive effect of cannabis. The former demonstrated robust evidence of the opioid-sparing effect of cannabis, but only one of the nine clinical studies demonstrated that effect, and the proof was of very low quality.

"found no evidence that cannabis use was associated with reduced opioid use or opioid cessation."[114]

That finding is consistent with the views of other experts.[115] A 2017 systematic review found that cannabis had a statistically insignificant palliative effect on chronic pain. As that study concluded, "Although cannabis is increasingly available for medical and recreational use, little methodologically rigorous evidence examines its effects in patients with chronic pain. Limited evidence suggests that it may alleviate neuropathic pain, but evidence in other pain populations is insufficient."[116] Data analytics performed by Gabriel Rada of the Epistomonikos Foundation, Chile, compiled from 1788 patients using cannabinoids for pain relief (15 studies) and from 3,489 patients in which cannabinoid-mediated side effects were recorded (29 studies), concluded that the certainty of evidence for pain relief was very low, and the certainty of evidence for adverse events was very high.[117]

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114. *Id.*; *see also* Humphreys & Saitz, *supra* note 98 ("The largest prospective study of cannabis as a substitute for opioids was a 4-year cohort study of 1514 patients with chronic pain who had been prescribed opioids. Cannabis use was associated with more subsequent pain, less self-efficacy for managing pain, and no reductions in prescribed opioid use. There was no substitution; rather, cannabis was simply added to the mix of addictive substances taken by patients with pain.").

115. *See* Hall et al., *supra* note 15, at 987 ("We find no evidence that medical marijuana laws (broadly specified) are associated with reductions in substance abuse or mortality. However, we find strong evidence that medical marijuana laws legalizing dispensaries reduce substance abuse treatments for opioids. Our estimates imply reductions in treatment admissions of over 15%, with even larger reductions suggested by synthetic control estimation. We also find evidence of reductions in opioid-related mortality. Our difference-in-differences estimate implies a 16% reduction in opioid-related mortality while synthetic control estimates imply even larger effects of 31% upon the adoption of legal medical marijuana dispensaries. In contrast to prior work (Bachhuber et al. 2014), we find this reduction only in states with dispensaries and not in the broader group of medical marijuana states. To explore potential mechanisms through which this policy might be working, we examine the influence of the medical marijuana policies on state-level opioid distribution. We find little evidence that states that legally protect medical marijuana dispensaries experience reductions in morphine dose equivalent amounts of opioids distributed to them. This result suggests that legalized medical marijuana distribution replaces illegal opioid acquisition and use, which is not reflected in the legal state supply of opioids."); *id.* at 988 ("Epidemiological studies of large samples of chronic pain patients have found that those who use cannabis do not use lower opioid doses than opioid users who do not use cannabis. A recent analysis of two waves of the US National Epidemiologic Survey on Alcohol and Related Conditions found that people who reported cannabis use at baseline were more (not less) likely to have an opioid use disorder 3 years later. This was also true among cannabis users who reported moderate to severe pain and opioid use at baseline."); Nugent et al., *supra* note 33, at 321 ("A 1-year prospective cohort study ($n = 431$) of patients with nociceptive and neuropathic chronic noncancer pain provides information about long-term treatment effects (50). Cannabis users had a reduction in average pain intensity (using a visual analogue scale from 0 to 10) that was stable across 4 time points over 1 year, but the change was small and not clinically significant (0.92 [CI, 0.62 to 1.23].").

116. Nugent et al., *supra* note 33, at 327–28.

117. Gabriel Rada, EPISTEMONIKOS FOUND., https://isof.epistemonikos.org/#/finding/593584b2e3089d0fec24dc01 [https://perma.cc/BP55-CAWD] (last visited May 29, 2019).

### 2. States with Liberal Marijuana Laws Should See Declining Opioid Overdose Rates, but They Do Not

If the advocates for marijuana as an opioid substitute or adjuvant for chronic, non-cancer pain relief were correct, we would expect by now to have seen a decrease in the number of opioid-induced fatal overdoses. After all, California adopted a medical marijuana program in 1996, and a majority of states now have such laws in place. Colorado legalized marijuana for all purposes in 2012, removing the last obstacle (a physician recommendation) to obtaining access to marijuana for medical or any other purpose. Yet, Colorado's opioid overdose death rates, opioid-related emergency department visits, hospitalizations, and use of naloxone to reverse an overdose have soared in the past few years.[118] At the start of the 2010–2016 period, the annual age-adjusted opioid death rate in legalizing and non-legalizing jurisdictions was the same, between 8.0 and 8.5 deaths per 100,000 people. Whereas the non-legalizing states subsequently had no increase in their opioid death rate until 2014, the legalizing jurisdictions' monthly rate increased steadily during 2010 through 2013. Thereafter, the legalizing jurisdictions' death rate distinctly accelerated, first by 16.4% per year and then by 33.5% per year as twelve more states approved medicinal marijuana and two more states and the District of Columbia approved recreational use. In the non-legalizing states, the opioid death rate increased during 2014 through 2016 but more slowly (16.4% per year) than in the legalizing jurisdictions. In 2016, the age-adjusted death rate was 18.2 per 100,000 people and 13.2 in the legalizing and non-legalizing jurisdictions, respectively. As of December 2016, the rate in the legalizing states and the District of Columbia was 52% higher than, and continuing to diverge from, the rate in non-legalizing states. Regression curves suggest that 20.34 (72%) of 28.19 additional deaths per 100,000 people during January 2010 through December 2016 occurred where marijuana was legalized.[119]

The Appendix to this article reprints a record of the number of opioid overdose deaths following the adoption of state medical marijuana laws. The data reveals that the number of opioid overdose deaths has increased in every state but one since that state legalized the medical use of marijuana. The one exception is Montana, yet the decrease from forty-five to forty-two deaths after medical marijuana legalization is too small to be probative, and the history of Montana's medical marijuana laws is too convoluted to be of much guidance.[120] To be sure,

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118. HEROIN RESPONSE WORK GROUP, HEROIN IN COLORADO: PRELIMINARY ASSESSMENT (2017), http://www.rmhidta.org/html/FINAL%20Heroin%20in%20Colorado%203.29.17.pdf [https://perma.cc/97UZ-MRR7].

119. CENTERS FOR DISEASE CONTROL AND PREVENTION, ABOUT MULTIPLE CAUSE OF DEATH, 1999-2016. CDC WONDER (2017), http://wonder.cdc.gov/mcd-icd10.html [https://perma.cc/ASL4-TYLM] (last visited May 29, 2019).

120. Archie Bleyer & Brian Barnes, *Opioid Death Rate Acceleration in Jurisdictions Legalizing Marijuana Use*, 178 JAMA INTERNAL MED. 1280 (2018). Montana has gone from pillar to post in its regulatory approach to medical marijuana, displaying dramatically different approaches to its regulation. Montana enacted a comprehensive drug law in 1969, and it prohibited all use or possession

correlation is not the same as causation; that data does not prove that medical marijuana laws cannot reduce opioid-related deaths. But it does justify skepticism.[121]

The 2014 and 2017 studies on which marijuana's advocates rely do not support the conclusion that smoking marijuana alleviates long-term non-cancer pain. Start with the 2014 study. It concluded that the fatal opioid overdose rate was approximately 25% lower in states with medical marijuana laws. The study compared the gross number of fatal opioid overdoses in states with and without medical marijuana laws. Finding evidence that the number is smaller in the former than in the latter,[122] the study concluded that medical cannabis laws are "associated with" lower opioid use mortality.[123]

That study, however, is subject to what is known as the Ecological Fallacy.[124] The study only compares the fatal overdose rates in states with and without

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of marijuana. In 2004, Montana voters passed a very liberal medical marijuana initiative. *See* MONT. CODE ANN. 50-46-102, 103 (2005) (repealed). By 2011, a large number of people had become authorized to use and distribute marijuana: nearly 20,000 users and shy of 4,000 "caregivers." In response, Montana revised its code in 2011, dramatically restricting the availability of medical marijuana by limiting to three the number of registered medical marijuana cardholders that any one business could serve. *See* The Montana Marijuana Act, Laws 2011, ch. 419, § 1 (as amended by 2016 Montana Laws Balt. Meas. 182 (I-182) § 3 (2016) (codified at MONT. CODE ANN. § 50-46-301 (2018)); Mont. Cannabis Indus. Ass'n v. Montana, 286 P.3d 1161, 1163 (Mt. 2012). Montana again revised its scheme in 2016. *See* 2016 Montana Laws Balt. Meas. 182 (I-182) § 3 (2016) (codified at MONT. CODE ANN. § 50-46-301 (2018)). *See generally* Thomas J. Bourguignon, Note, *Montana Cannabis Industry Association v. State of Montana and the Constitutionality of Medical Marijuana*, 75 MONT. L. REV. 167, 170–74 (2014) (discussing the pre-2016 history of Montana's regulation of medical marijuana). Given the back and forth in Montana law and the short period that the newest statute has been in effect, Montana does not offer a good basis for drawing any conclusions regarding the potential opioid-sparing effect of cannabis.

121. *Compare* Bradford et al., *supra* note 59; Wen & Hockenberry, *supra* note 59 (both finding lower opioid prescription rates in states with medical marijuana laws), *with* Bleyer & Barnes, *supra* note 120, at 1281 (2018) ("The opioid crisis appears to be worsening where marijuana has been legalized, despite fewer opioid prescriptions, and as such, constitutes evidence for the gateway hypothesis and against the marijuana protection hypothesis. In any event, before other states rush to legalize marijuana and risk worsening the opioid crisis, the marijuana-opioid interaction should be more definitively researched."), *and with* Ashley C. Bradford et al., *Opioid Death Rate Acceleration in Jurisdictions Legalizing Marijuana Use: Response*, 178 JAMA INTERNAL MED. 1281 (2018), *and* Jason Hockenberry & Hefei Wen, *Opioid Death Rate Acceleration in Jurisdictions Legalizing Marijuana Use: Response*, 178 JAMA INTERN. MED. 1282 (2018) (both defending initial studies).

122. Interestingly, the raw numbers indicated a higher overdose mortality rate in states with medical marijuana laws than in those without. *See* Bachluber, *supra* note 60, at 1670 ("The mean age-adjusted opioid analgesic overdose mortality rate increased in states with and without medical cannabis laws during the study period. . . . Throughout the study period, states with medical cannabis laws have a higher opioid analgesic mortality rate. . . . "). Only a time-adjusted regression model showed that states with medical marijuana laws has a lower overdose mortality rate. *Id*. at 1669.

123. *Id*. at 1670 ("In the adjusted model, medical cannabis laws were associated with a mean 24.8% lower annual rate of opioid analgesic overdose deaths [with a 95% confidence internal] . . . compared with states without laws."), 1671 ("In an analysis of death certificates from 1999 to 2010, we found that states with medical cannabis laws had lower mean opioid analgesic overdose mortality rates compared with states without such laws.").

124. *See, e.g*., W.S. Robinson, *Ecological Correlations and the Behavior of Individuals*, 38 INT'L J. OF EPIDEMIOLOGY 337 (2009).

medical marijuana programs. An association between two facts, however, does not establish a causal relationship between them. For example, a number of key variables between states were not considered in the study: the availability of naloxone as a rescue agent; treatment slots for opioid use disorder ("OUD"); medications to treat OUD; the supply of fentanyl (currently the leading cause of death from opioids), which varies widely geographically; access to heroin and the range of heroin price and purity in different states; incarceration rates; and other factors. A lower rate of prescription opioid overdoses in states with medical marijuana laws may also conceivably be attributable to state guidelines that discourage opioids for patients with a positive drug screen for illegal substances including marijuana.[125]

A simple example makes that point. Suppose that there is a positive correlation between ice cream sales and the number of drownings in a state. That relationship does not prove that eating ice cream causes drownings. In all likelihood, ice cream sales are higher in the warmer summer months, which is also when more people go swimming.[126] That hypothetical explains why group-wide results cannot substitute for individual correlations.[127] Accordingly, any correlation noted in the 2014 study does not prove that state adoption of medical marijuana laws will lead to a reduction in fatal opioid overdoses.

The 2017 study sought to offset those flaws by controlling for state differences in population, income, education, ethnicity, prescription monitoring programs (viz., state laws allowing pharmacies to access the opioid prescriptions supplied for an individual by other pharmacies, to prevent a patient from "double dipping"), the presence of authorized marijuana distribution dispensaries, and the distribution of naloxone.[128] Even factoring in those considerations, the 2017 study

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125. *See* Humphreys & Saitz, *supra* note 98 ("The methodological concern with such studies is that correlation is not causation. Many factors other than cannabis use may affect opioid overdose deaths, such as prescribing guidelines, opioid rescheduling, Good Samaritan laws, incarceration practices, and availability of evidence-based opioid use disorder treatment and naloxone. Furthermore, the aggregate population associations (e.g., between medical cannabis and opioid overdose) maybe opposite of those seen within individuals. In the only individual-level analysis, which included 57146 people aged 12 and older, of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.").

126. Hall et al., *supra* note 15, at 987.

127. *See* Boehnke, *supra* note 20, at 740 ("Although suggestive that cannabis could act as a replacement or alternative for opioids, this finding [in Bachluber, *supra* note 60] was on an ecological level, so changes at an individual level could not be gauged."); Robinson, *supra* note 124, at 340–41 ("The relation between ecological and individual correlations which is discussed in this paper provides a definite answer as to whether ecological correlations can validly be used as substitutes for individual correlations. They cannot. While it is theoretically possible for the two to be equal, the conditions under which this can happen are far removed from those ordinarily encountered in data. From a practical standpoint, therefore, the only reasonable assumption is that an ecological correlation is almost certainly not equal to its corresponding individual correlation.").

128. *See, e.g.*, Bryce Pardo, *Do More Robust Prescription Drug Monitoring Programs Reduce Prescription Opioid Overdose?*, 112 ADDICTION 1773 (2016); Powell et al., *supra* note 8. Another recent study—Louisa Degenhardt et al., *Experience of Adjunctive Cannabis Use for Chronic Non-Cancer Pain: Findings from the Pain and Opioids IN Treatment (POINT) Study*, 147 DRUG & ALCOHOL DEPENDENCE 144 (2015)—involved oral reports by participants of the pain-reduction effect of cannabis.

found somewhat conflicting evidence that state medical marijuana laws did reduce fatal overdoses.[129]

Yet, even that study did not account for a variety of other potentially confounding factors such as state-by-state and statewide inequalities in the distribution of naloxone, inequalities in the availability of emergency medical services across different states or within any one of them in their capacity to provide naloxone, or inequalities in the existence of prescription monitoring programs that seek to limit access to opioids by recording prescriptions.[130] Atop those considerations is an additional factor that should be considered: state policy toward imprisonment of opioid abusers. If individuals are imprisoned for a considerable period of time, people addicted to opioids lose their tolerance to those drugs. Once tolerance is lost, they can fatally overdose if they use the same amount of an opioid after being released from custody that they had regularly consumed before their confinement.[131]

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129. *See* Nugent et al., *supra* note 33, at 327–28.

130. *See, e.g.*, Hall et al., *supra* note 15, at 988; Saxon & Browne, *supra* note 15, at 4. One psychiatrist criticized the 2014 study as follows:

> So what is causing the decrease in opioid overdoses? A 2015 Rand Corporation study gives us a big clue. When their researchers adjusted Bachhuber's calculations for race and unemployment rates, the difference between medical and non-medical marijuana states became insignificant. Other scientists have also linked opioid deaths to employment and race. According to Brookings Institute research published this year, middle-aged white men with no college degree are dying in unexpectedly high numbers, especially from opioid overdose. These are the non-Hispanic white Americans who feel society has left them behind. They're often out of work or under-employed. And they tend to live in non-medical marijuana states. Oklahoma, Indiana, Ohio, West Virginia and much of the South have some of the lowest rates of college education and some of the highest rates of opioid use in the country. None have legalized medical marijuana. In contrast, three-fourths of the medical marijuana states were in the half of the country with the highest rates of college graduates. So medical marijuana states have fewer opioid overdoses because they have fewer non-college educated white men. It has nothing to do with marijuana. Other research has come at this issue from the opposite direction—does marijuana increase the risk of opioid addiction?—with disquieting findings. A study published this summer in the American Journal of Psychiatry found that teenage marijuana users were twice as likely to progress to opioid abuse. I see this at work. My heroin-addicted patients almost all used marijuana in their early teens. And there are far more teenage marijuana users in medical marijuana states. According to the National Survey on Drug Use and Health, the 20 states with the highest rates of teen use all have medical marijuana laws. So thanks to medical marijuana and legalization laws, the country has far more teenage marijuana users, and these kids are far more likely to get addicted to drugs like oxycodone and heroin. Legalized marijuana makes the opioid epidemic more severe and more intractable.

Ed Gogek, Opinion, *Marijuana Is Not the Answer to Opioids*, PINAL CENTRAL (Dec. 18, 2017), https://www.pinalcentral.com/opinion/columns/gogek-marijuana-not-the-answer-to-opioids/article_9ba3cbcf-c3ac-5c4d-be60-26d18f047ecd.html [https://perma.cc/QX4X-3F5S].

131. *See* Hall et al., *supra* note 15, at 987. Certain studies have argued that medical marijuana laws lead to a reduction in opioid use by pointing to a decrease in Medicare and Medicaid opioid prescriptions in states with such laws. *See supra* note 59. Those studies are subject to many of the same criticisms voiced in the text regarding the 2014 and 2017 reports. In addition, there is reason to believe that physicians often prescribed opioid painkillers for people on the federal disability rolls because federal rules for hospital reimbursement are based on a set of factors that included patients' subjective reaction to how well physicians treated their pain. The result was to spur physicians to prescribe opioids more often than they would have found strictly necessary. *See* ANNA LEMBKE, DRUG DEALER, MD (2016). Perhaps, the decrease in opioid prescriptions reduced unnecessary opioid scripts.

Furthermore, even if there were a beneficial effect from the adoption of state medical marijuana laws, that effect has diminished over time and now is statistically insignificant.[132] The 2014 and 2017 studies considered data from 1999–2010 and from 1999–2013, respectively. Whatever descriptive and predictive power those studies might have had before 2013 is gone today. This is because the fatal overdose epidemic has mutated since 2013.[133]

The current epidemic of fatal opioid overdoses is the third of three different "waves" that have broken on America's shores, and each wave is characterized by a more powerful opioid than its predecessors.[134] Wave 1 was the overuse of prescription opioids. In Wave 2, pharmaceutical firms developed abuse-deterrent formulations of opioids, and the federal and state governments made it more difficult for physicians to prescribe opioids for chronic pain sufferers. That wave saw people turn to heroin use, as heroin was easier to obtain and less expensive than prescription opioids. Wave 3, the current stage, is beset with use of fentanyl and its derivatives (e.g., carfentanil, a tranquilizer used on elephants) as a cutting agent added to heroin because fentanyl is less expensive to create.[135] The result is

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132. R. Vincent Pohl, Time Trends Matter: The Case of Medical Cannabis Laws and Opioid Overdose Mortality 3 (June 7, 2018) (unpublished manuscript), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3192703 [https://perma.cc/4AVA-ZQ4D].

133. *Id*. at 25 ("I estimate the impact of MCL and active and legal medical cannabis dispensaries and find that it is sensitive to the inclusion of state-specific time trends. This finding implies that the common trends assumption that is necessary for DD regressions to deliver unbiased estimates is violated. The estimated effects also vary with the sample period. As more recent years are added, the impact of MCL generally diminishes, suggesting that they may have worked in reducing opioid-related mortality in the early years of the opioid crisis but to a lesser extent as the crisis has become more severe in recent years. Hence, MCL may not be as successful in alleviating the opioid crisis as previously found.").

134. *See Understanding the Epidemic*, CTRS. FOR DISEASE CONTROL & PREVENTION (Dec. 19, 2018), https://www.cdc.gov/drugoverdose/epidemic/index.html [https://perma.cc/SFQ6-RLKF]; SAM QUINONES, DREAMLAND: THE TRUE TALE OF AMERICA'S OPIATE EPIDEMIC (2016); Mark A.R. Kleiman, *A Primer on Fentanyl(s)*, NYU MARRON INST. OF URBAN MGMT. (May, 25, 2018), http://marroninstitute.nyu.edu/blog/a-primer-on-fentanyls [https://perma.cc/X4SG-3VQ8] ("The synthetic opioids—usually referred to both in the press and by law enforcement as 'fentanyl'—have now outstripped not only the prescription opioids such as oxycodone but also heroin in terms of overdose deaths, and . . . the trend line is almost vertical."); Josh Sanburn, *Heroin Is Being Laced with a Terrifying New Substance: What You Need to Know about Carfentanil*, TIME (Sept. 12, 2016), http://time.com/4485792/heroin-carfentanil-drugs-ohio/ [https://perma.cc/9SJX-BSH3] ("A drug so powerful that it's used to sedate elephants is finding a new, illicit use laced into heroin . . . . The drug, called Carfentanil, is a synthetic opioid so strong that just a few granules the size of grains of table salt can be lethal."). To offer an example as to the relative strengths of opioids, consider this. Morphine is the baseline painkiller and has a value of 1. Hydrocodone, which is sold under the brand name Vicodin, is also a 1. Oxycodone, which is sold as Percocet and OxyContin, is 1.5, meaning that it is 1.5 times as strong as morphine. Heroin is 4–5 times as strong as morphine. Fentanyl, 50–100. Carfentanil, 10,000–100,000. Kleiman, *supra*. Smaller and smaller amounts of heroin, fentanyl, and carfentanil can prove fatal.

135. Fentanyl is also being added to other street drugs, such as cocaine, and is another cause of overdose deaths in unsuspecting people. *See* DRUG ENF'T ADMIN., DEA BULL. NO. 039-18, DEADLY CONTAMINATED COCAINE WIDESPREAD IN FLORIDA (2018), https://www.dea.gov/sites/default/files/2018-07/BUL-039-18.pdf [https://perma.cc/87W2-HYZ8]; Salman A. Klar et al., *Notes from the Field: Furanyl-Fentanyl Overdose Events Caused by Smoking Contaminated Crack Cocaine—British Columbia, Canada, July 15–18, 2016*, 65 MORBIDITY & MORTALITY WKLY. REP. 1015 (2016).

that even if state medical marijuana laws had a beneficial effect at the time of the original studies, those state laws no longer have that effect today.

Finally, a recent study should put the kibosh on the argument that medical cannabis regimens can offset opioid overdose mortality. Using the same methods as the authors of the 2014 study but with seven additional years of data included (2010–2017, as well as the 1999–2010 data used in the 2014 study), the authors found that states with medical marijuana programs had an increase in opioid deaths.[136] That is, although the 2014 study found a 4.8% reduction in opioid overdose deaths per 100,000 population in states with a medical cannabis program, the recent study found a *22.7% increase* in overdose deaths for the same population when you enlarge the data base by considering the results from 2010 to 2017.[137]

In sum medical marijuana laws are not the answer to today's opioid problem. As one scholar has recently summarized:

> [P]olicies that may have been effective in the early years of the opioid epidemic are no longer successful in reducing the number of overdose deaths. Mortality rates have not only grown faster in recent years than in the 2000s, but also the type of opioids most commonly associated with overdose deaths has shifted from prescription opioids to heroin and more recently to synthetic opioids such as fentanyl. In this evolving public health crisis, it is therefore crucial to re-evaluate policy responses.[138]

### 3. Individuals Using Marijuana for Pain Relief Do Not Exhibit a Reduction or Elimination of Opioid Use

The prevalence of concurrent use of marijuana and opioids ranges from 8.9 to 31.8%. There is evidence that some people who supplement their opioid use with cannabis increase their opioid use without obtaining their sought-after pain relief.[139] A 2017 study led by Doctor Olfson found that "[i]n a nationally representative

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136. Chelsea L. Shover et al., *Association between Medical Cannabis Laws and Opioid Overdose Mortality Has Reversed over Time*, PNAS (June 10, 2019), https://www.pnas.org/content/pnas/early/2019/06/04/1903434116.full.pdf [https://perma.cc/7688-VT32].

137. *Id*. at 1.

138. *See* Pohl, *supra* note 132, at 3–4.

139. *See* Cooper et al., *supra* note 15, at 6 ("Overall, these findings demonstrate opioid-sparing effects of cannabis for analgesia that is accompanied by increases in some measures of abuse liability."); Degenhardt et al., *supra* note 128, at 146 ("Those who had used cannabis for pain reported higher pain severity, greater interference from and poorer coping with pain, and more days out of role in the past year, compared to those who had not used [marijuana]."); Shannon M. Nugent et al., *Patterns and Correlates of Medical Cannabis Use for Pain Among Patients Prescribed Long-Term Opioid Therapy*, 50 GEN. HOSP. PSYCHIATRY 104, 108 (2018) ("patients prescribed [long-term opioid therapy] were at greater risk for prescription opioid misuse"); Mark Olfson et al., *Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States*, 175 AM. J. PSYCHIATRY 47, 49–50 (2018); Marian Wilson et al., *Cannabis Use Moderates the Relationship between Pain and Negative Affect in Adults with Opioid Use Disorder*, 77 ADDICTIVE BEHAVIORS 225 (2018) (concluding that cannabis use strengthens, rather than weakens, the relationship between pain and depression or anxiety).

sample of adults evaluated at wavers 3 years apart, cannabis use was strongly associated with subsequent onset of nonmedical prescription opioid use and higher levels of opioid use disorder compared with non-marijuana users."[140]

For example, consider an evaluation conducted at a community-based pain management center of the relationship between cannabis use and aberrant drug behaviors in noncancer pain patients receiving chronic opioid therapy. Patients who tested positive for cannabis use in their initial random urine drug toxicology were more likely to abuse opioids and wind up in a higher level of clinical monitoring of opioid medication use.[141] The authors concluded that concurrent use of cannabis and opioids by patients with chronic pain appears to indicate higher risk for opioid misuse. Medical cannabis users had higher scores of risk for prescription opioid misuse (but, ironically, not for nicotine use or hazardous alcohol use). The authors concluded that there are potential risks associated with co-occurring long-term opioid therapy and medical cannabis for pain.[142] Another study correlated pain patients' use of marijuana and other drugs and found that marijuana users who did not use other drugs consumed significantly more opioids and reported higher pain scores than non-marijuana users. In patients who used other drugs, there were no differences in opioid consumption or pain scores. They concluded that chronic marijuana use might require greater opioid use to alleviate pain.[143] Medical marijuana users were also significantly more likely to report

140. Olfson et al., *supra* note 139, at 49–50. Although that study focused on recreational marijuana users, the distinctions between users of marijuana for purported medical or recreational purposes are not clear. *See* Olfson et al., *supra* note 101. More than a third of medical marijuana users used recreational marijuana in a primary care setting. The similarities between medical and recreational marijuana users (e.g., similar psychiatric symptom and behavior comorbidity, use of multiple drugs in addition to marijuana) are robust, proportional differences are small, with many participants in these groups more alike than different. A higher use of marijuana with opioids alone, both prescription and nonprescription, was also a defining feature of the medical users and is consistent with these participants having greater pain, reduced mobility, and more medical problems. A lower rate of prescription opioid overdoses in state with medical marijuana laws might indicate that marijuana is being used treat pain in place of opioids, or to lower the dose of opioids, but also might be attributable to state opioid prescription guidelines that discourage opioids for people with a positive drug screen, including marijuana. A different study reported similarities between medical marijuana users and nonmedical marijuana users except that medical marijuana users were more likely to have used cocaine. This overlap compromises the claims of medical marijuana advocates, as marijuana use would make a bad situation worse for chronic pain sufferers. Other research points in the same direction. *See* Wilson M. Compton et al., *Use of Marijuana for Medical Purposes Among Adults in the United States*, 317 JAMA 209 (2017); Alan C. Osborne et al., *Self-Reported Medical Use of Marijuana: A Survey of the General Population*, 162 CMAJ 1685 (2000); Gary M. Reisfield et al., *The Prevalence and Significance of Cannabis Use in Patients Prescribed Chronic Opioid Therapy: A Review of the Extant Literature*, 10 PAIN MED. 1434 (2009); Peter Roy-Byrne et al., *Are Medical Marijuana Users Different from Recreational Users? The View from Primary Care*, 24 AM. J. ADDICTION 599 (2015).

141. *See* DiBenedetto et al., *supra* note 33.

142. *See* Nugent et al., *supra* note 139.

143. *See* Salottolo et al., *supra* note 33, at 22–23 ("The primary findings from this pilot study suggest that marijuana use significantly affects acute pain management and results in increased consumption of opioid analgesics and greater self-reported pain following traumatic injury, especially in patients who did not report using other drugs. . . . These preliminary data suggest that marijuana use, especially chronic use, may affect pain response to injury by requiring greater frequency and dosing of opioid analgesia.").

medical use and nonmedical use of prescription drugs in general, with elevated risks for pain relievers, stimulants, and tranquilizers.[144]

### 4. The Concomitant Use of Marijuana and Opioids Conceivably Interferes with Treatment for Opioid Use Disorder

Another important consideration is whether the use of marijuana interferes with treatment for opioid use disorder. Marijuana users at the onset of OUD treatment and those continuing heavy marijuana use during treatment were at increased risk of dropping out before completing treatment.[145] Others have reported that marijuana use among individuals with alcohol or other drug dependence is associated with lower odds of achieving abstinence from drugs (including opioids) and heavy alcohol use.[146]

* * * * *

The bottom line is this: The scientific studies conducted to date do not prove that the crude, plant form of cannabis can substitute for opioids for treatment of acute or chronic pain.[147] Nor do they prove that marijuana can satisfactorily serve as an adjunctive therapy, particularly given its side effects.[148] There is increasing evidence that marijuana is a companion drug, rather than a substitute for

144. Theodore L. Caputi & Keith Humphreys, *Medical Marijuana Users Are More Likely to Use Prescription Drugs Medically and Nonmedically*, 12 J. ADDICTION MED. 295 (2018).

145. Alexandra M. Franklyn et al., *The Impact of Cannabis Use on Patients Enrolled in Opioid Agonist Therapy in Ontario, Canada*, PLOS ONE (Nov. 8, 2017), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0187633 [https://perma.cc/B44Q-58ZW].

146. Mohammadali Mojarrad et al., *Marijuana Use and Achievement of Abstinence from Alcohol and Other Drugs Among People with Substance Dependence: A Prospective Cohort Study*, 42 DRUG & ALCOHOL DEPENDENCE 91 (2014). There is no reported difference in that regard between medical and recreational marijuana use.

147. *See, e.g.*, Jessica S. Merlin et al., *Marijuana Use Is Not Associated with Changes in Opioid Prescriptions or Pain Severity Among People Living with HIV and Chronic Pain*, 81 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME 231, 234 (2019) ("We did not find evidence that marijuana use in PLWH [People Living with HIV] is associated with improved pain outcomes, or reduced opioid prescribing."); *id*. at 232–34.

148. *See, e.g.*, Humphreys & Saitz, *supra* note 98, at 639 (2019) ("Recent state regulations (e.g., in New York, Illinois) allow medical cannabis as a substitute for opioids for chronic pain and for addiction. Yet the evidence regarding safety, efficacy, and comparative effectiveness is at best equivocal for the former recommendation and strongly suggests the latter—substituting cannabis for opioid addiction treatments is potentially harmful. Neither recommendation meets the standards of rigor desirable for medical treatment decisions."); *id*. at 640 ("Cannabis and cannabis-derived medications merit further research, and such scientific work will likely yield useful results. This does not mean that medical cannabis recommendations should be made without the evidence base demanded for other treatments. Evidence-based therapies are available. For chronic pain, there are numerous alternatives to opioids aside from cannabis. Nonopioid medications appear to have similar efficacy, and behavioral, voluntary, slow-tapering interventions can improve function and well-being while reducing pain. For the opioid addiction crisis, clearly efficacious medications such as methadone and buprenorphine are underprescribed. Without convincing evidence of efficacy of cannabis for this indication, it would be irresponsible for medicine to exacerbate this problem by encouraging patients with opioid addiction to stop taking these medications and to rely instead on unproven cannabis treatment.").

opioids.[149] Marijuana use increased the number of opioid users, including patients being treated for pain, and marijuana use decreases the likelihood of successful treatment for opioid use disorder and possibly even contributes to the epidemic. There is some evidence that a portion of patients have reduced opioids and resorted to marijuana, but population-wide, they are not in the majority.

Nonetheless, some individual cannabinoids (or a combination of them) might prove to be a useful adjunctive therapy.[150] The FDA has already concluded that non-psychoactive, non-addictive cannabidiol passed muster as a treatment for childhood forms of epilepsy. Preclinical research has shown that cannabidiol inhibits the rewarding effects of opioids, whereas THC can enhance opioid reward or have no effect.[151] Cannabidiol might show that it or other cannabinoids in botanical marijuana, separately or in combination, have therapeutic uses in the opioid crisis and for other disorders. The critical question today, however, is whether we can rely on plant marijuana to solve our epidemic of fatal opioid overdoses. The answer is "no."

## IV. WHERE DO WE GO FROM HERE?

The number of opioid-caused fatalities over the last decade is a national nightmare. It justifies President Donald Trump's characterization of it as a public health emergency.[152] It would be tempting for Congress to follow the lead of most states and revise the Controlled Substances Act of 1970 to permit marijuana to be used for medical purposes in states that approve that practice. Supporters of liberalized marijuana laws would urge Congress to treat this subject, like most other issues dealing with the practice of medicine, as a matter best left to the

149. Kenneth Finn, *Why Marijuana Will Not Fix the Opioid Epidemic*, 115 MO. MED. 191 (2018).

150. *See supra* note 41 and accompanying text.

151. *See* Katsidoni et al., *supra* note 85, at 286 ("Our results suggest that cannabidiol interferes with brain reward mechanisms responsible for the expression of the acute reinforcing properties of opioids, thus indicating that cannabidiol may be clinically useful in attenuating the rewarding effects of opioids."); Stopponi et al., *supra* note 80; Cadoni et al., *supra* note 80; Marcello Solinas et al., *Cannabinoid Agonists but Not Inhibitors of Endogenous Cannabinoid Transport or Metabolism Enhance the Reinforcing Efficacy of Heroin in Rats*, 30 NEUROPSYCHOPHARMACOLOGY 2046 (2005) ("Under a progressive-ratio schedule, however, THC dose-dependently increased the number of 50 mug/kg heroin injections self-administered per session and the maximal ratio completed (break-point), with peak increases at 1 mg/kg THC. In addition, 1 mg/kg THC increased break-points and injections self-administered over a wide range of heroin injection doses (25-100 microg/kg), indicating an increase in heroin's reinforcing efficacy and not its potency."); *but see* David R. Maguire & Charles P. France, *Effects of Daily Delta-9-Tetrahydrocannabinol Treatment on Heroin Self-Administration in Rhesus Monkeys*, 2 BEHAVIORAL PHARMACOLOGY 249 (2016) ("Daily treatment with Δ-THC (0.01-0.1 mg/kg/12 h, subcutaneously) either had no effect on or decreased responding for heroin' [albeit at a lower dose than example above.]").

152. *See* Presidential Memorandum on Combating the National Drug Demand and Opioid Crisis, 82 Fed. Reg. 50,305 (Oct. 31, 2017); *Ending America's Opioid Crisis*, WHITEHOUSE.GOV, https://www.whitehouse.gov/opioids/ [https://perma.cc/W8SG-6QXW] (last visited May 26, 2019); U.S. DEP'T OF HEALTH & HUMAN SERVS., DETERMINATION THAT A PUBLIC HEALTH EMERGENCY EXISTS (Oct. 26, 2017), https://www.hhs.gov/sites/default/files/opioid%20PHE%20Declaration-no-sig.pdf [https://perma.cc/6FXR-6P4F].

states to decide. Of course, if Congress went along with that approach, those supporters would perceive any such revision of federal law as the high-water mark in their longstanding campaign to liberalize access to cannabis. Whether that reaction is in the public interest is another matter entirely.

Members of Congress should resist such simple-minded responses. Just as it would be a mistake to quickly pass some half-baked legislative "solution" simply to appear to respond to this epidemic,[153] it would also be a mistake to deny the scientific evidence and create an exception to the approach that federal law has taken for eighty years regarding the legitimacy of drugs.[154] In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act. The Act prohibited the distribution in interstate commerce of adulterated drugs and directed the FDA Commissioner to decide what drugs can be sold in interstate commerce.[155] In 1962, Congress reiterated that delegation by directing the Commissioner to bar the interstate sale of drugs that have not yet been proved effective.[156] For more than fifty years, American law, policy, medicine, and society have accepted the need for the medical and scientific professionals at the FDA to decide what is a drug, whether that drug is safe and effective, and, if so, how to regulate its use. We should leave those responsibilities to the FDA, rather than create a newfangled exception for marijuana in the mistaken attempt to bring the opioid overdose crisis to a close.

Statutes can be just as difficult to amend or repeal as they are to enact, so Congress should pass a law only after serious deliberation over the need for that statute, its scope, likely effect, costs, and benefits, as well as any alternatives that could be foregone or delayed through passage of a mistaken law. Most importantly, Congress cannot and should not only listen to and respond to advocates,

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153. *See* Bleyer & Barnes, *supra* note 120, at 1280 ("cannabis policy has raced ahead of cannabis science") (citation and internal punctuation omitted); Paul Terpeluk, *Should 'Medical Marijuana' Be Recommended for Patients? Why Our Answer Is 'No'*, CLEVELAND CLINIC (Jan. 10. 2019), https://health.clevelandclinic.org/should-medical-marijuana-be-recommended-for-patients/ [https://perma.cc/3YGE-MBKK] ("We at Cleveland Clinic, however, will not be recommending 'medical marijuana' for our patients. . . . In the world of healthcare, a medication is a drug that has endured extensive clinical trials, public hearings and approval by the U.S. Food & Drug Administration (FDA). Medications are tested for safety and efficacy. They are closely regulated, from production to distribution. They are accurately dosed, down to the milligram. Medical marijuana is none of those things.") (internal punctuation omitted); Rebecca Voelker, *States Move to Substitute Opioids with Medical Marijuana to Quell Epidemic*, 320 JAMA 2408, 2409–10 (2018) ("Methadone, buprenorphine, and naltrexone are approved by the US Food and Drug Administration (FDA) for opioid use disorder along with counseling and psychosocial support. Evidence supporting their use 'is just so compelling,' said [Jeffrey] Selzer, MD, chair of the Public Policy Committee for the American Society for Addiction Medicine]. The drugs 'successfully treat addiction due to opioids, they prevent overdose, they result in much fewer complications related to opioid use disorder's assorted health consequences—things like HIV seroconversion—and there's really no evidence that medical marijuana would do the same,' Selzer added.").

154. *See* Paul J. Larkin, Jr., *States' Rights and Federal Wrongs: The Misguided Attempt to Label Marijuana Legalization Efforts as a "States' Rights" Issue*, 16 GEO. J.L. & PUB. POL'Y 495 (2018).

155. *See id*. at 499–500.

156. *See id*.

for it was advocates (financial, patient, political, or otherwise) that created the opioid crisis in the first place.

At the same time, absence of proof of the effectiveness of cannabinoids is not the same as proof of its absence. That cannabinoids found in the marijuana plant or synthesized de novo have not yet been shown to be useful as analgesics does not mean that no such evidence will be forthcoming. The major challenge in this endeavor is identifying compounds with therapeutic effects at doses and pharmacological targets that do not produce intoxication, cognitive impairment, psychotomimetic effects, psychosis, amotivational syndrome, or cognitive degradation after long term use for chronic pain. Marijuana has been a Schedule I controlled substance for nearly fifty years, and there are a variety of steps that research scientists take in order to obtain the federal government's authorization to conduct research into the therapeutic benefits of cannabinoids. Further scientific study of the issue is warranted.[157] As two commentators have noted, cannabinoids "certainly do show some promise as medications for chronic pain and possibly other conditions and definitely deserve considerably more investigation."[158] We agree.[159] The American Medical Association certainly believes so. As several investigators noted in 2017 in the *Journal of the American Medical Association: Psychiatry*, "[F]urther research is needed to investigate how marijuana is consumed by those who use it for medical reasons, including doses, frequency, routes of administration, and concurrent use

157. *See* Anuj Shah et al., *Impact of Medical Marijuana Legalization on Opioid Use, Chronic Opioid Use, and High-risk Opioid Use*, J. GEN. INTERNAL MED. 6 (forthcoming 2019) ("These results suggest that MML could be one policy tool that may modestly decrease opioid use; chronic and high-risk opioid use in a landscape where pain management options are limited and opioid misuse and addiction are rising rapidly. However, more research on the health benefits of marijuana is required and future analyses weighing the potential benefits of decreased likelihood of opioid use with the potential risks of MML such as increased prevalence of mental health disorders and misuse of marijuana need to be conducted.").

158. *See* Saxon & Browne, *supra* note 15, at 5 ("Numerous small controlled studies have repeatedly demonstrated that certain cannabinoids do reduce acute and chronic pain when compared to placebo in double-blind designs. Most of these trials have use[d] pharmaceutical forms of cannabinoids, either dronabinol (oral THC), nabilone (an oral, synthetic THC analog) or an extract of plant cannabis containing nearly equal proportions of THC and cannabidiol delivered as an oral mucosal spray, although a few have used smoked or vaporized marijuana. Most of the trials have relatively small sample sizes and used crossover designs over brief periods. One study of an oral mucosal spray did have an open-label extension to 52 weeks with reported continuing benefits. In all the studies, the cannabinoids had a worse side effect profile than the placebo that sometimes included measurable cognitive adverse events. In one study nabilone was less efficacious than dihydrocodeine but had more problematic side effects."); *see also, e.g.*, Hayes & Brown, *supra* note 15, at 1674 ("The potential protective role of medical marijuana in opioid-analgesic-associated mortality and its implication for public policy is a fruitful area for future work.").

159. *See* Carlton, *supra* note 13 ("Dr. Andrew Epstein, an oncologist at memorial Sloan Kettering Cancer Center in New York, and an American Society of Clinical Oncology (ASCO) patient care expert, said. . . . 'We need a lot more research to clearly state whether or not medical marijuana can treat cancer pain as effectively as opiates,' [Dr.] Epstein said. 'I think it's a helpful adjunct to pain medicines, [but] I do not think there are data to suggest or even show that they are just as good.").

of other substances, including alcohol."[160] In fact, that year the National Institutes of Health awarded a five-year grant to researchers at the Albert Einstein College of Medicine and Montefiore Health System to determine the analgesic value of medical cannabis for chronic pain.[161] We should at least wait for the results of that study before legislating a solution to the opioid problem. Above all, we must carefully weigh the benefits compared to the risks of adverse side effects.

## CONCLUSION

The crude form of smokable marijuana cannot provide an escape hatch from today's opioid overdose epidemic by serving as a substitute for opioids or as an opioid-sparing adjunctive medication. The FDA will never approve that delivery system as a medical device nor will it approve an undefined marijuana plant as a drug. One or more individual cannabinoids, however, might someday prove valuable in the alleviation of pain. In fact, the FDA has already demonstrated its willingness to approve cannabinoids for therapeutic uses, by approving cannabidiol for the treatment of rare, childhood forms of epilepsy and THC for chemotherapy-induced nausea and AIDS wasting. Studies conducted to date do not establish that cannabinoids can usefully resolve the affliction suffered by those with chronic pain in a manner that avoids harmful side effects. Until we reach the point at which science can confidently say that cannabinoids are a proper analgesic substitute for opioids, physicians will need to rely on an array of analgesics (opioid and non-opioid) and other types of alternatives to medication for pain relief. Pain patients are also being encouraged to assume that perfection in pain relief is not always possible and coping with certain forms of pain is feasible.

Additional research might help us reach the point where a range of alternative non-opioid medications and non-pharmacological treatments can alleviate suffering. Congress should eliminate any unreasonable roadblocks that keep science from reaching that goal and should even go further by actively encouraging research to learn of new possible targets. Any such bills deserve serious consideration on an urgent basis. If isolated cannabinoids can, in fact, help control the opioid overdose epidemic, we should be in a hurry to learn about it. But we are not there yet. Accordingly, we cannot justify basing today's public policy decisions regarding the proper classification of the marijuana plant as a controlled substance on its usefulness as an analgesic substitute for opioids.

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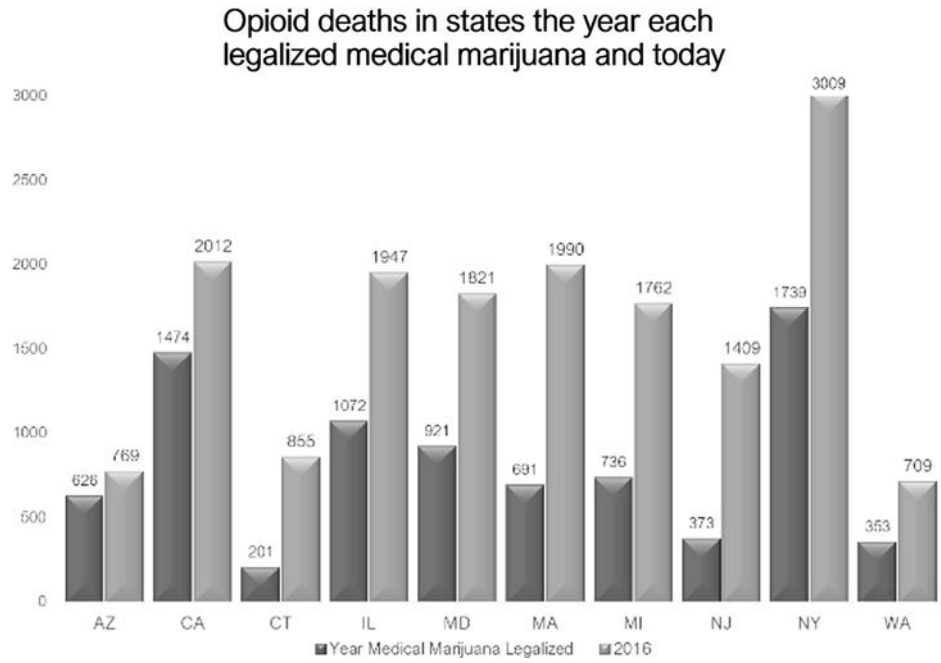
160. Compton et al., *supra* note 34, at 560.

161. TREY WILLIAMS, *A Government Health Agency Is Funding the First-Ever Study on Medical Marijuana's Impact on Opioid Abuse*, MARKET WATCH (Aug. 12, 2017), https://www.marketwatch.com/story/a-government-health-agency-is-funding-the-first-ever-study-on-medical-marijuanas-impact-on-opioid-abuse-2017-08-11 [https://perma.cc/YRZ7-UG2A]; *see also* Yasmin L. Hurd & Charles P. O'Brien, *Molecular Genetics and New Medication Strategies for Opioid Addiction*, 127 AM. J. PSYCHIATRY 935 (2018).

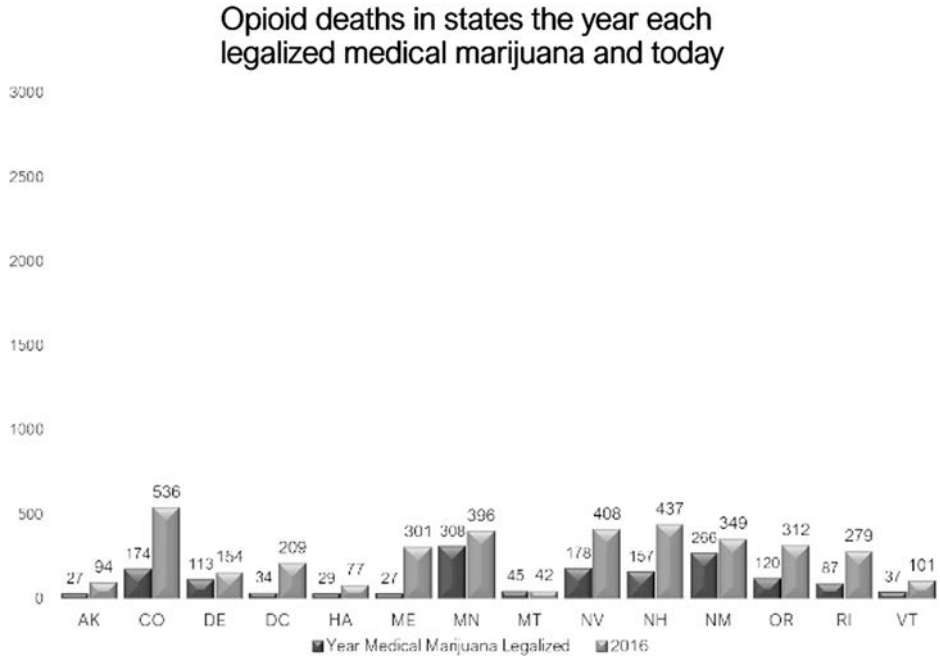
APPENDIX[162]

FIGURE 1.




162. MARIJUANA REP., NAT'L FAMILIES IN ACTION (June 20, 2018), https://us2.campaign-archive.com/?u=2138d91b74dd79cbf58e302bf&id=72d3823ea1 [https://perma.cc/7MLG-TMLS] ("Data source: The Kaiser Family Foundation analyzed opioid death data collected by the Centers for Disease Control and Prevention from 1999 through 2016.").

FIGURE 2.


Opioid deaths in states the year each legalized medical marijuana and today
3000
2500
2000
1500
1000
500
0
27
94
174
536
113
154
34
209
29
77
27
301
308
396
45
42
178
408
157
437
266
349
120
312
87
279
37
101
AK
CO
DE
DC
HA
ME
MN
MT
NV
NH
NM
OR
RI
VT
Year Medical Marijuana Legalized
2016