

United States Marijuana Legalization and Opioid Mortality Trends Before and During the First Year of the COVID-19 Pandemic

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Abstract

To determine if marijuana legalization reduced opioid mortality, the U.S. opioid and fentanyl subset death trends during the 2010-2019 decade were compared in states and District of Columbia (D.C.) (jurisdictions) that had implemented marijuana legalization with states that had not. Acceleration of opioid mortality during 2020, first year of the COVID-19 pandemic, was also compared in recreational and medicinal-only legalizing jurisdictions. Joinpoint methodology was applied to Centers for Disease Control and Prevention WONDER data. Trends in legalizing jurisdictions were cumulative aggregates. The overall opioid and fentanyl death rates and percentage of opioid deaths due to fentanyl increased more during 2010-2019 in jurisdictions that legalized marijuana than in those that did not (pairwise comparison $p = 0.007$, 0.05 , and 0.006 , respectively). By 2019, the opioid and fentanyl death rates were 44% and 50% greater in the legalizing than non-legalizing jurisdictions, respectively. When the COVID-19 pandemic hit in 2020, jurisdictions that implemented recreational marijuana legalization before 2019 had significantly greater increases in both overall opioid and fentanyl death rates than jurisdictions with medicinal-only legalization. For all opioids, the mean (95% confidence interval [CI]) 2019-to-2020 increases were 46.5% (95% CI, 36.6% to 56.3%) and 29.1% (95% CI 20.2% to 37.9%), respectively ($p = 0.02$). For fentanyl, they were 115.6% (95% CI, 80.2% to 151.6%) and 55.4% (95% CI, 31.6% to 79.2%), respectively ($p = 0.01$). Marijuana legalization is correlated with worsening of the U.S. opioid epidemic, and especially during the COVID-19 pandemic with recreational legalization.

Keywords: marijuana medicinal legalization; marijuana recreational legalization, U.S. opioid mortality epidemic; fentanyl; COVID-19 pandemic

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

Introduction

As of 2022, most states and the District of Columbia (D.C.) [jurisdictions] in the U.S. had legalized medicinal marijuana (cannabis),¹ including 20 jurisdictions that legalized recreational use, 12 of which did so during 2019-2022.² The pressure for the federal government to remove its prohibition of marijuana sales and use and to leave their regulation to state law-makers is increasing, including “moving past the *gateway hypothesis* of drug use”.³ In October, 2022, the President pardoned federal convictions for simple marijuana possession offenses.⁴ By 2026, sales of legal recreational cannabis the U.S. are predicted to reach 37 billion dollars⁵ and the potential economic benefit has incentivized jurisdiction legalization.⁶

The U.S. also has the world’s 2nd highest cannabis-use-disorder prevalence and, by far, the world’s highest opioid death rate.⁷ To assess whether or not these two grim statistics are related, as considered by others,^{8,9} we previously compared the opioid death rate in the composite aggregate of legalizing jurisdictions with that in non-legalizing jurisdictions.⁷ With then too few evaluable recreational-legalizing jurisdictions, we did not assess them for differences in the impact of recreational versus medicinal legalization. In this study, we update all 50 states and D.C. during the last decade (2010-2019) by comparing opioid mortality rates in jurisdictions states that had or had not by start of 2019 legalized marijuana for all opioids and the fentanyl group of synthetic opioids. Because, as described in the Methods section, the COVID-19 pandemic distinctly changed prior opioid mortality trends, we also analyzed the first calendar year of the COVID-19 pandemic that began in 2020 with the latest available data and compared it with the prior calendar year, 2019.

Methods

Data Sources and Analytic Methods.

Age-adjusted opioid death data in the U.S. were obtained from CDC WONDER.¹⁰ For multiple calendar-year analysis, trends were determined with Joinpoint Regression Program version 4.9.1.0,¹¹ applying weighted least squares, logarithmic transformation, and standard errors provided by the Program. The Joinpoint Regression Program identifies when a trend changes to another trend, the average annual percent change (AAPC) and p-values for each trend detected, and relative comparison of concomitant trends via pairwise

comparison with either parallel or non-parallel methodology, for which we selected the latter. T-tests used for comparisons assumed unequal variances.

International Classification of Disease (ICD).

ICD codes for accidental poisoning (X40-X44), intentional self-poisoning (X60-X64), and other poisoning (Y10-Y14) were used in conjunction with following opioid T-Codes: T40.0 opium, T40.1 heroin, T40.2 other opioids, T40.3 methadone, T40.4 fentanyl and its semisynthetic derivatives, T40.6 other synthetic narcotics.

These categories include morphine, hydromorphone, oxycodone, fentanyl, the semisynthetic fentanyl moieties, heroin, opium, codeine, meperidine, methadone, propoxyphene, tramadol, and other/unspecified

narcotics. Because of the dramatic increase in fentanyl deaths such that by 2017 accounted for the majority of opioid deaths (Fig. 1), this category (T40.4) was also separately analyzed and referred to a *potent fentanyl*, inclusive of the more potent semisynthetic derivatives.

Pre- and Intra Pandemic COVID-19 Analyses.

With the onset of the COVID-19 pandemic in 2020, the opioid mortality trends in the U.S. distinctly accelerated (Fig. 1). The opioid death rate increased 37.6% from 2019 to 2020, 7 times more than the average of the prior 3 years, 5.4% (Fig. 1 upper panel). Every month in 2020 after the pandemic began in March was the highest ever recorded (Fig. 1 lower panel). The 2019 to 2020

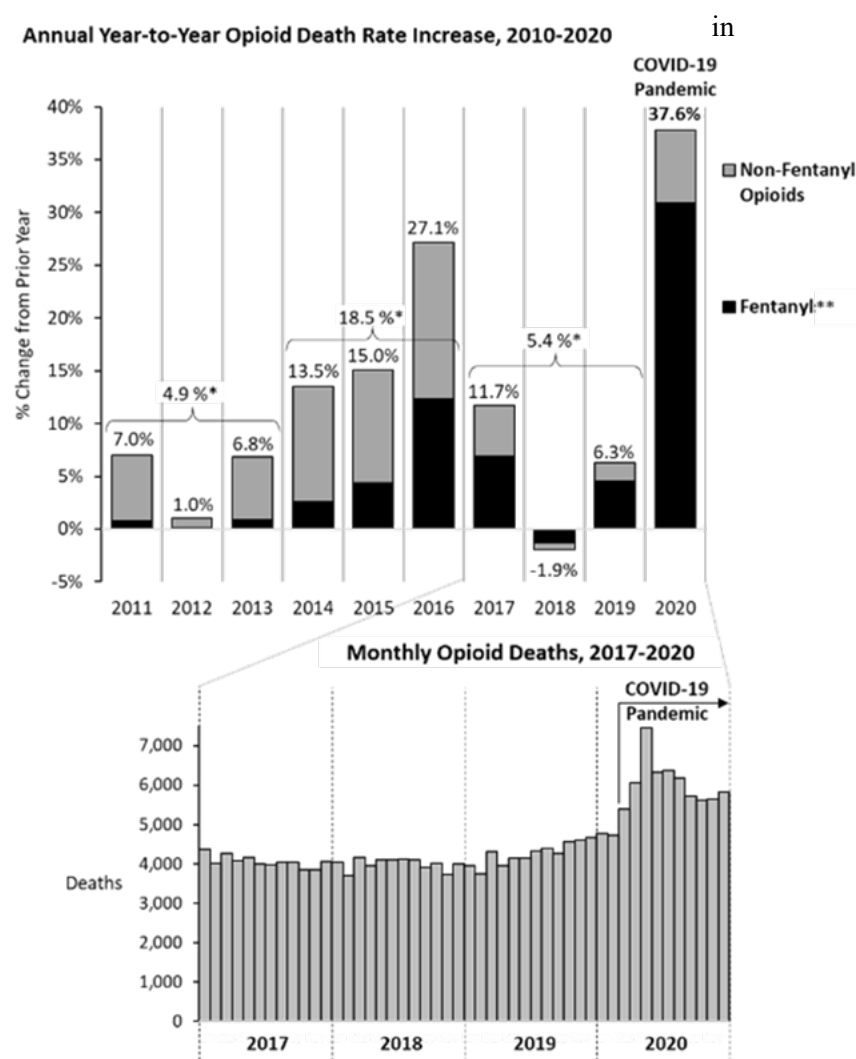


Figure 1 Annual Change (from year before) in Opioid Death Rate, 2010-2020, U.S., and by Portion due to Fentanyl (black zones).**
 Labeled percentages are increases in all opioid deaths from year before.
 * Percentages above horizontal brackets are 3-year averages.
 ** Includes semisynthetic fentanyl
 Data Source: CDC WONDER¹⁰

acceleration occurred in all 50 state and D.C. jurisdictions except New Hampshire. Hence, we compared the 1st year of the pandemic, 2020, with the prior year.

Jurisdiction Classification

Supplemental Table S1 lists each state and D.C. by whether and when marijuana legalization for medicinal or recreational use was implemented, and the reference sources.^{12,13,14,15,16,17,18,19,20,21,22} As of the start of 2019, 28 jurisdictions (27 states and D.C.) had implemented marijuana legalization and 23 states that had not, as shown at the top of Figures 2 and 3 and listed in Supplemental Table S1. The legalizing group mortality trend was determined via cumulative aggregate, beginning in 2020 with those that had already implemented legalization and adding the legalizing jurisdiction thereafter during the year it implemented legalization. Georgia, North Carolina, South Carolina, Texas and Wisconsin were included in the non-legalizing group since they legalized only CBD oil for medicinal use and primarily for epilepsy. Arkansas was not included in the legalizing group since medicinal licenses were not statewide until 2020 (Supplemental Table S1).

For recreational legalization analysis, the 7 states and D.C. that implemented recreational use before 2019 were compared with 20 states that had implemented medicinal, but not recreational, use. Three states that implemented recreational use during 2019-2020, Michigan, Massachusetts and Maine, were considered within the medicinal legalization group since their recreational legalization implementation occurred too recently to expect a recreational-legalization-specific effect, especially with the dramatic increase in all but one jurisdiction during the first year of the pandemic. A sub-analysis that excluded these 3 states from the medicinal group was also conducted. Similarly, West Virginia, which implemented medicinal legalization during 2019-2020, was primarily excluded from the legalizing jurisdictions groups but also sub-analyzed as in it. Using year of legalization enactment itself instead of the year of implementation of legalization accentuated the difference in overall opioid results and did not significantly alter the fentanyl results.⁷ Difference-in-difference methodology was unnecessary to compare subsequent trends since the rates in the two groups were nearly identical for the initial three years of comparison.

Results

Pre-pandemic Trends

The opioid death rate in the U.S. began to increase at a statistically-significant rate in 2014 (Fig. 2), after jurisdictions began to legalize recreational use of marijuana, with Colorado and Washington as the first two states, in 2012-2013. Thereafter, the opioid death rate increased significantly more rapidly in legalizing jurisdictions, at an AAPC of 20.2 ($p = 0.04$) during 2013-2016 and 10.2 ($p = 0.02$) during 2016-2019, in contrast to an AAPC of 15.3 ($p = 0.02$) during 2013-2017 and no increase during 2017-2019 (AAPC = 0.3, $p = 0.91$) in non-legalizing jurisdictions (Fig. 2). By 2019, the opioid death rate was 44% greater in the legalizing than non-legalizing group. Over the 2010-2019 decade, pairwise comparison was highly statistically significant ($p = 0.007$) (Fig. 2).

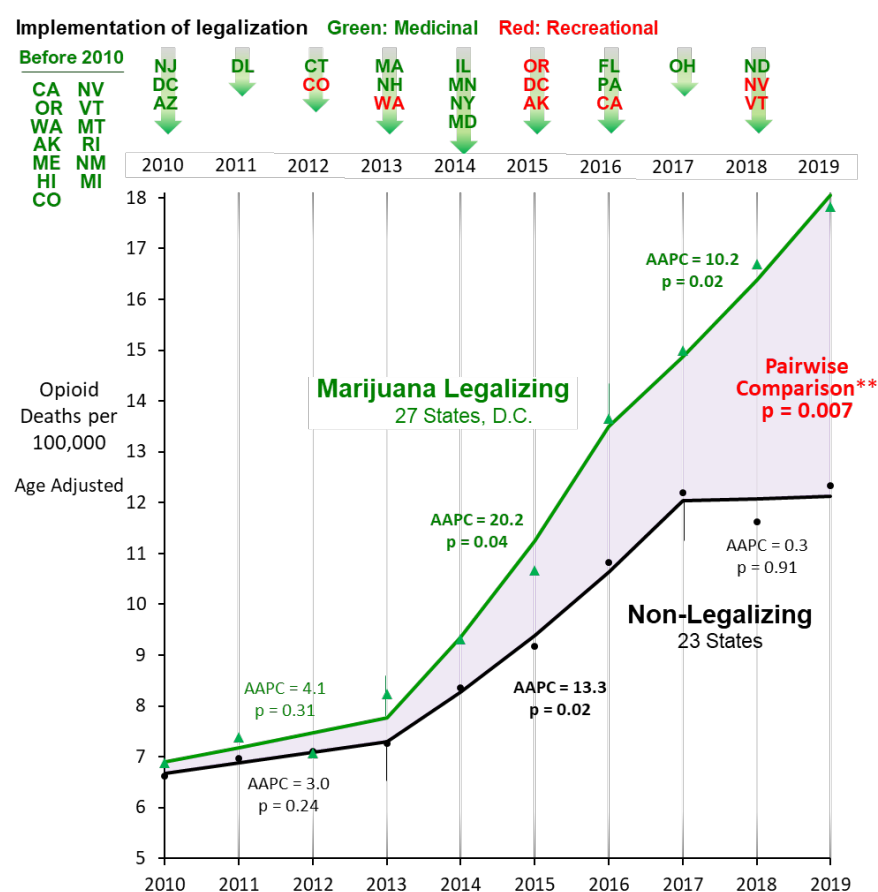


Figure 2. Joinpoint/AAPC* Analysis of Annual Opioid Death Rates, 2010-2020, U.S., of Non-Legalizing Jurisdictions (black data) and Cumulative Aggregate of Legalizing Jurisdictions as of 2019 (green data)

* AAPC – average annual percent change

** Joinpoint non-parallel pairwise comparison analysis

Data Source: CDC WONDER¹⁰ and updated from Bleyer A, Barnes B, Finn K⁷

The potent fentanyl death rate also increased after recreational use of marijuana began during 2012-2013, especially in legalizing jurisdictions (Fig. 3). During 2013-2016, the increase was twice as fast in legalizing than non-legalizing jurisdictions, and during 2017-2019 it continued to rise at a rate that was statistically significant ($p = 0.002$) whereas it slowed to a non-statistically significant rate increase in non-legalizing jurisdictions ($p = \text{NS}$) (Fig. 3 upper panel). By 2019, the potent fentanyl death rate was 50% greater in the legalizing than non-legalizing jurisdictions, at 13.9 and 7.8 per 100,000 respectively, and the total increase during 2000-2019 was greater in the legalizing jurisdictions (pairwise comparison $p = 0.05$) (Fig. 3 upper panel). During 2010-2019, there were a greater percentage of opioid deaths due to fentanyl (pairwise comparison $p = 0.006$) (Fig. 3 lower panel). By 2019, the proportion of opioid deaths due to potent fentanyl was 80% in legalizing jurisdictions and 63% in non-legalizing jurisdictions (Fig. 3 lower panel).

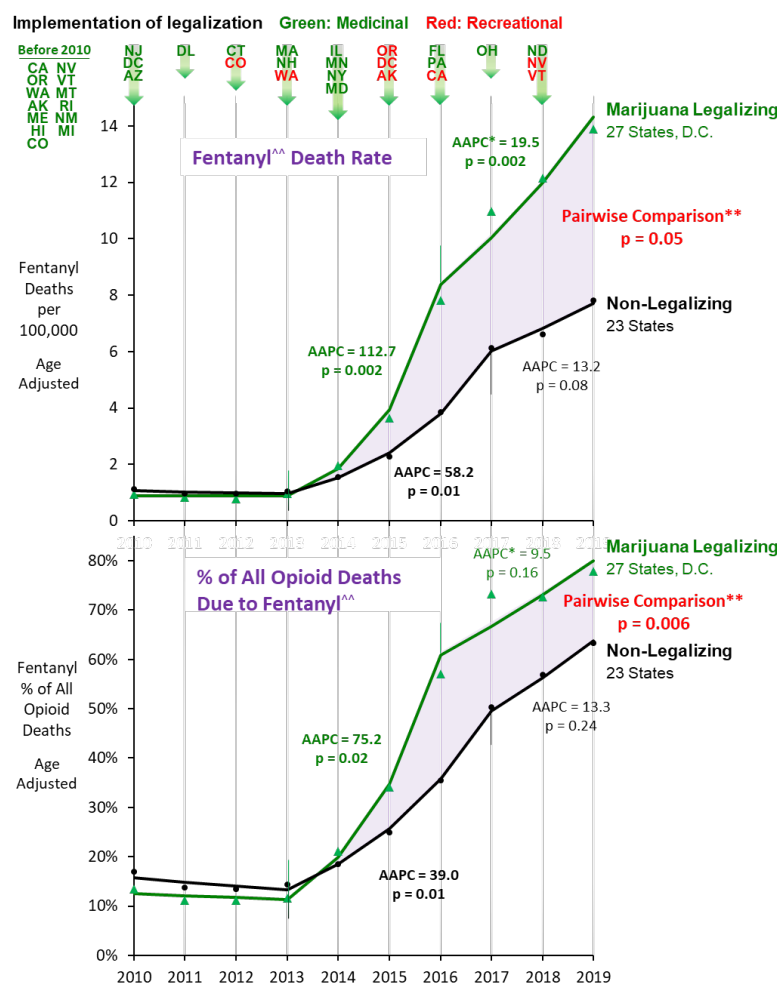


Figure 3. Joinpoint/AAPC* Analysis of Pre-Pandemic Annual Mean Fentanyl Death Rate (upper panel) and % of All Opioid Deaths due to Fentanyl (lower panel), 2010-2019, U.S., Non-Legalizing Jurisdictions (black data) vs. Aggregate of Legalizing Jurisdictions as of 2019 (green data).

* AAPC – average annual percent change

** Joinpoint non-parallel pairwise comparison analysis

^^ Includes semisynthetic fentanyl

Data Source: CDC WONDER¹⁰

First-Year Pandemic Trends

When the COVID-19 pandemic distinctly accelerated the opioid death rate, the 8 jurisdictions that implemented legalization of recreational marijuana before 2019 (Fig. 4 red data) had, as a group, a 30.4 absolute % greater increase than the 20 jurisdictions that implemented medicinal but not recreational legalization (57.7% vs. 27.3%) (Fig. 4 green data). At the jurisdiction level, the opioid death rate was greater in recreational-legalizing than medicinally-legalizing jurisdictions ($T = 2.22$, $p = 0.02$), with mean (95% C.I.) increases of 46.5% (36.6%, 56.3%) and 29.1% (20.2%, 37.9%), respectively (Fig. 4).

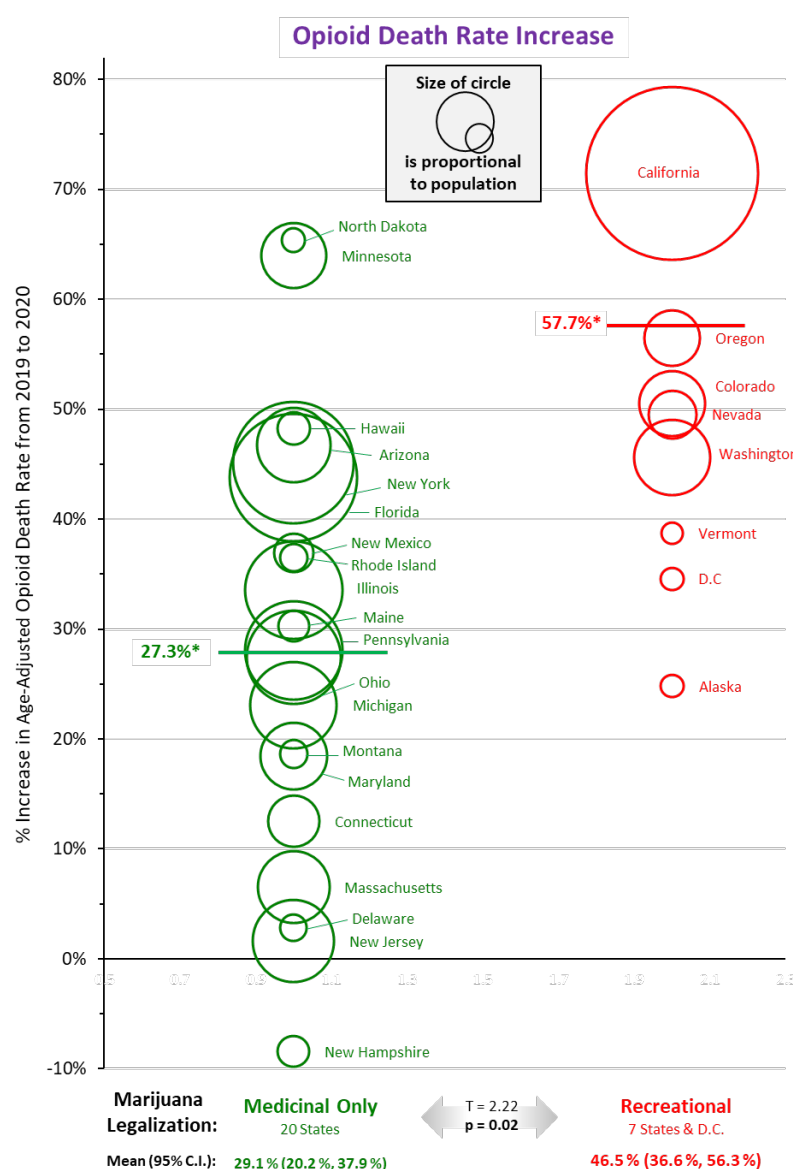


Figure 4. Increase in Opioids Death Rate from 2019 to First Year of Pandemic, 2020, by Recreational and Medicinal Only Legalizing Jurisdictions.

* Group mean (jurisdictions combined)

Data Source: CDC WONDER¹⁰

For potent fentanyl, the death rate in the recreational legalization jurisdictions accelerated at an 87.1 absolute % greater increase than in jurisdictions that implemented medicinal but not recreational legalization (123.3% vs. 36.2%) (Fig. 5). At the jurisdiction level, the opioid death rate was also greater ($T = 2.69$, $p = 0.01$) for recreational-legalizing jurisdictions than the medicinally-legalizing jurisdictions, with mean (95% C.I.) increases of 115.6% (80.2%, 151.6%) and 55.4% (31.6%, 79.2%), respectively (Fig. 5).

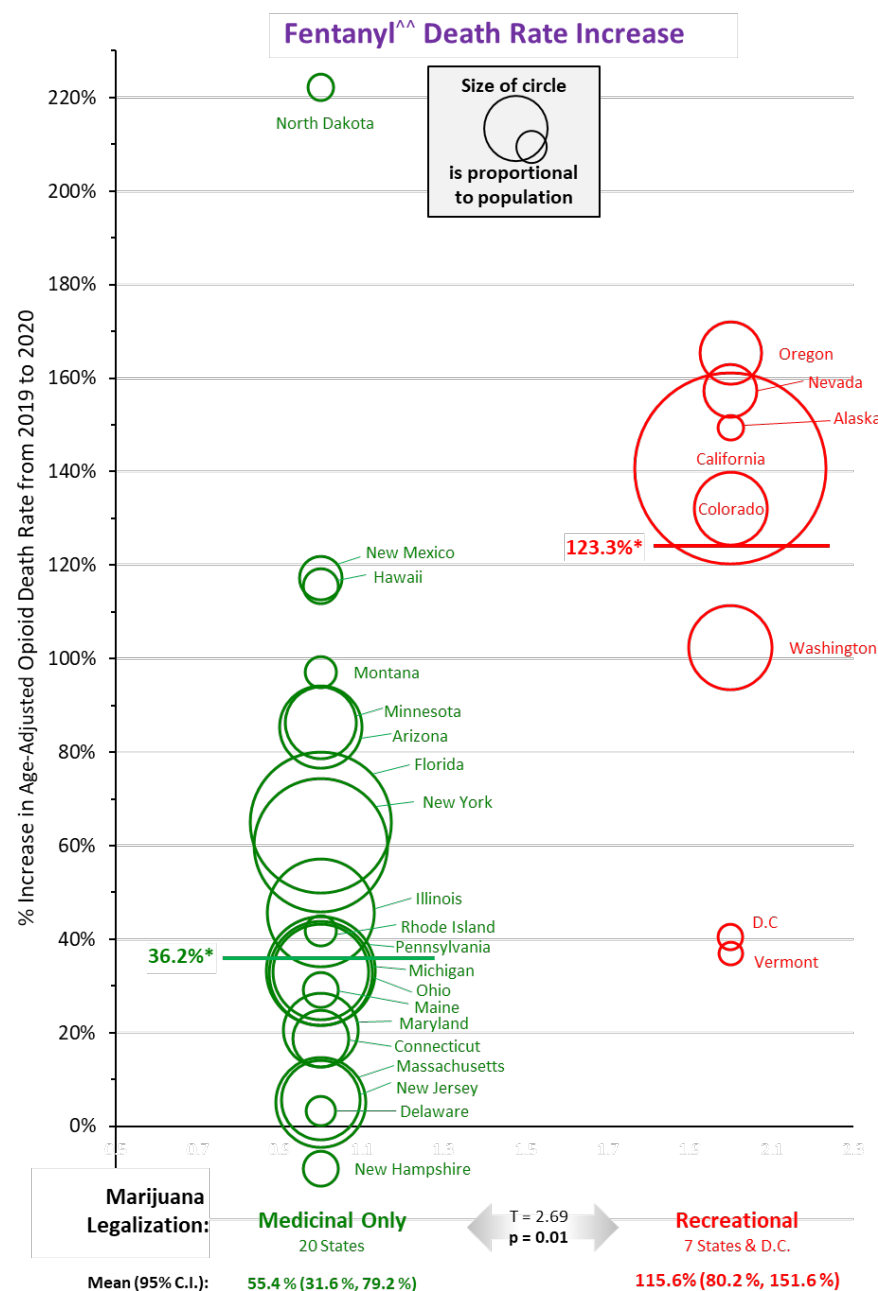


Figure 5. Increase in Fentanyl^{^^} Death Rate from 2019 to First Year of Pandemic, 2020, by Recreational and Medicinal Only Legalizing Jurisdictions.

* Group mean (jurisdictions combined) ^{^^} Includes semisynthetic fentanyl
Data Source: CDC WONDER¹⁰

If the 3 states that began recreational legalization during 2019-2020, Maine, Massachusetts, and Michigan, are removed from the medical legalizing group, the recreational legalizing group still had a statistically-significant greater increase for both all opioids ($T = 2.20, p = 0.02$) and the fentanyl group of opioids ($T = 2.39, p = 0.02$). If the state that began medicinal legalization during 2019-2020, West Virginia, is included in the medical legalizing group, the recreational legalizing group continued to have a statistically-significant greater increase for both all opioids ($T = 2.25, p = 0.02$) and potent fentanyl ($T = 2.74, p = 0.01$). California is the state with the largest population and greatest increase in opioid death rate. Excluding it from the recreational legalization group did not eliminate the statistically-significant greater opioid death rate increase in the recreational than medical legalizing jurisdictions for either opioids in general ($T = 2.27, p = 0.02$) or the fentanyl group of opioids ($T = 2.38, p = 0.02$).

Discussion

As analyzed, U.S. state and D.C. data suggest that marijuana legalization has been associated with worsening of opioid mortality, whether primarily due to conventional opioids or to the fentanyl group of opioids. The most recent trend indicates that recreational-use legalization is associated with a greater opioid mortality increase. If so, jurisdictions that have legalized marijuana have contributed disproportionately to the country's opioid crisis.

Evidence for Biologic Mechanism of Marijuana Legalization Increasing Opioid Mortality

That marijuana legalization may lead to opioid use is biologically plausible via a *gateway* mechanism since cannabinoids act in part via opioid receptors.²³ Cannabinoids also increase dopamine concentrations.^{24,25}

Clinical evidence for gateway sequencing has been reported in multiple studies. In the U.S., 9% of adults progressed to other illicit drug use during the second year after first marijuana use, 36% within a decade, and nearly half thereafter.²⁶ Non-medical prescription opioid use and opioid use disorder increased nearly 6- and 8-fold, respectively within 3 years of marijuana use.²⁷ Medical marijuana use was positively associated with greater use and misuse of prescription opioids.²⁸ Self-reported marijuana use during injury recovery was associated with a subsequent increased amount and duration of opioid use.²⁹ In New York State, opioid use

was found to approximately double on days when marijuana was used.³⁰ In a national database of prescription claims, opioid-naïve patients who were marijuana users undergoing lumbar spinal fusions had a higher risk of developing post-operative opioid dependence than non-marijuana users, despite having decreased daily dosages of opioids.³¹ A similar pattern was observed in Boston.³² Among college students, marijuana users were 12 times more likely to use opioids than non-users and higher levels of marijuana use was associated with greater likelihood of using opioids.³³ Among Maryland students followed for 12 years after elementary school, marijuana at age 14 was associated with more frequent use of opioids at age 19.³⁴ Among Los Angeles high-school students, each of five different marijuana products was associated with subsequent initiation of illicit drug use, including heroin, and of prescription opioids.³⁵ Among pregnant women, the rate of opioid-related treatment admissions was 2.5 fold greater in states that legalized medicinal marijuana.³⁶ Most recently, evidence from national surveys indicate that Americans with cannabis use disorder had nearly 7 times the odds of also having opioid use disorder³⁷ and that after 2-3 years of recreational legalization the frequency of misusing prescription opioids increases.³⁸

Other countries have had similar evidence. In Canada, marijuana use was found to lead to premature withdrawal from opioid addiction treatment programs.³⁹ In Australia, a 4-year prospective-cohort study of 1,514 patients with chronic non-cancer pain, those who used marijuana daily or near-daily used more opioids than those who did not.⁴⁰ A meta-analysis of 6 studies in Australia, New Zealand and U.S. between 1977 and 2017 indicated that transitioning from marijuana to opioid use, abuse or dependence was 2.5-2.8 times greater than in non-marijuana users.⁴¹

Prior Studies of Marijuana Legalization's Effect on Opioid Mortality

Initial reports based on a limited number of U.S. states suggested that marijuana legalization reduced opioid mortality.^{13,42,43} One of these reports was based on 2006-2011 data, before the subsequent acceleration of opioid mortality.⁴⁴ A report in 2018 concluded that medical marijuana legalization was associated with a 30% reduction in Schedule III opioid Medicaid prescriptions.⁴⁵ Two county-level studies in states that allowed marijuana dispensaries to operate had lower opioid- mortality rates in counties with medical and recreational dispensaries,^{46,47} albeit the county-level methodology utilized has been negatively critiqued.^{7,48}

At the national level, an update of aforementioned studies by other investigators indicates that legal medical marijuana is associated with higher opioid mortality, particularly when available through retail dispensaries, and that recreational marijuana may be correlated with greater death rates relative to the counterfactual of no legal cannabis.⁴⁹ Opioid overdose death rates during 2012-2017 in states that legalized medicinal marijuana had a greater increase in opioid mortality than in those that did not ($p < 0.01$).⁵⁰ In Massachusetts, Maine, Nevada and California, per-capita opioid-related emergency department visit rates initially decreased in states that legalized recreational use but began to increase within 6 months after legalization,⁵¹ as of the last year of data in 2017 and before most recreational-legalizing jurisdictions had an acceleration in their opioid mortality.⁷

In Colorado, three studies have not supported the initial impression of a marijuana legalization benefit on opioid mortality,^{52,53,54} one of which not only found that the original analysis did not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from -21% to +23% and remained positive after accounting for recreational cannabis laws.⁵² Another had opioid-related ER visits and admissions to the Colorado Hospital Association increase 51% and 45%, respectively, during the first 4 years after recreational legalization.⁵⁴ In Washington and Colorado, hospital admissions for opioid substance abuse did not decrease during the first 2-4 years, during 2013-2017, after recreational legalization.⁵⁵ In Washington state, recreational marijuana legalization was not followed by a reduction in opioid compliance rate in patients treated with opioids for chronic pain during the first year after recreational legalization.⁵⁶ As we previously reported, the opioid mortality increase in these both Colorado and Washington two states began after 2017 and more than 2 years after recreational legalization.⁷

Limitations

The most important limitation of our study is its ecological design that does not establish causation. Factors other than marijuana legalization may have resulted in marijuana legalizing jurisdictions having a higher opioid death rate. Most notably, legalizing jurisdictions may be more substance use/abuse/dependent-oriented and thus the local culture may be responsible for both, rather than marijuana legalization exacerbating opioid mortality. Legalizing and non-legalizing jurisdictions may differ in socioeconomic status, race/ethnicity, and medical, psychosocial, and psychiatric diagnoses that may have caused more opioid deaths in legalizing

jurisdictions. In that opioid use disorder is a “disease of despair” brought about by economic hardship, the economic issue is particularly concerning, albeit the 2020 gross domestic product per capita in the legalizing states we previously analyzed was greater than in the non-legalizing states.⁷ As to the greater opioid mortality increase during the pandemic in recreationally-legalizing jurisdictions, several were states that considered marijuana businesses as “essential” and allowed to remain open whereas drug treatment programs were closed and more opioid-use-disorder patients were unable to access care.

The most contradictory report relative to our analysis is a study of recreational marijuana-legalizing states of Colorado, Washington, Oregon, Alaska, Nevada, California, and Massachusetts that found they had an 11% average (range 3%-28%) reduction in opioid overdose fatalities.⁵⁷ This study did not include 2020 when the opioid mortality increased the most and that we specifically evaluated, did not compare the opioid mortality rate in recreational states with either medicinal-only or non-legalizing states, and did not include D.C.

Another study that counters our findings is a review of individual opioid prescriptions during 2011-2018 that associated recreational and medicinal cannabis access laws with fewer morphine milligram-equivalents and total days’ supply of opioids prescribed, number of patients receiving opioids, and probability a provider prescribes any opioids net of any offsetting effects.⁵⁸

Strengths

The current investigation also has several advantages over prior reports. It adds 9, 6, 4, 2, and 2 additional follow-up years to the prior studies.^{13,42,43,44,46, respectively} Compared to the most recently reported state-level analysis⁴⁴ that analyzed 2000-2011 data, it includes data up to 2020. A prior report also showed a reversal of initial benefit of marijuana legalization to worsening opioid mortality.⁵² Our analysis of their data shows a divergence in the opioid death rates during 2012-2017 that is similar to what we observed during those years (Fig. 2). Our study adds two more years of data and D.C., and also differs in that our control group was states that had not legalized marijuana whereas their control group began with all states and excluded those that legalized when they did. Also, we included separate analyses of the T40.4 category of fentanyl and semi-synthetic analogues and we included heroin and opium that were either not assessed in prior studies^{13,54,59} or specified.^{28,43}

Conclusions

At the jurisdiction level in the U.S., marijuana legalization during the past decade was associated with a greater acceleration in the opioid death rate. During the first year of the COVID-19 pandemic, the opioid mortality acceleration occurred significantly more in jurisdictions that legalized recreational marijuana than in those that legalized medical, but not recreational, use. A strikingly greater increase in marijuana sales during the pandemic may have contributed to an even greater increase in the country's opioid mortality epidemic during its 2nd year and, possibly, years subsequent to the pandemic.⁶⁰

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