Cannabis in Medicine

An Evidence-Based Approach

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Equo ne credite, Teucri. Quidquid id est, timeo Danaos et dona ferentes
– Publius Vergilius Maro, 19 B.C.

Medicus necesse est dicere quod possit ex antecedentibus, quia praesens et futura dicamus - haec medium est, et in intuitu obiecti specialem duo de morbo, scilicet facere bonum non est non nocere
– Hippocrates, Of the Epidemics, 400 B.C.

Dedicated to those who have been affected or have lost loved ones to any substance of abuse and addiction, including marijuana, and to the memory of Peggy Mann, and other pioneers, not afraid to speak the truth.

Foreword

Losing Ground: The Rise of Cannabis Culture

Addressing the Wider Implications of Increasing Marijuana Use

Why Our Knowledge of the Risks in Cannabis Exposure Has Increased

As ongoing science enhances our understanding of the health risks of cannabis/marijuana exposure, two dimensions of the problem have been revealed. First, the range of health concerns has grown. Second, our confidence has grown that the risk lies in the impact of cannabis exposure itself, as an independent variable, rather than in a constellation of potential confounders.

To be sure, genetic propensity and co-morbidity issues affect the risk of cannabis exposure, placing some populations at higher risk than others, but the exposure to cannabis has a clear effect on the course of the propensity and/or the expression of the co-morbidity over and above the simple fact of a predisposition.

More broadly, of the known health concerns that were visible in research over the past 20 years (to pick an arbitrary period), it is reasonable to argue that few have been allayed or disconfirmed, while the majority of concerns have been not only confirmed but, in several instances, rendered even more worrisome, fraught, and widespread in terms of populations affected and the severity of the effects.

Results are surely still contested, but in general cautions are increasingly becoming questions more of the persistence and depth of the effects, rather than rejection of the validity of strong correlations between cannabis exposure and increased risk of negative effects.

Studies increasingly support some attributional role to the elements of cannabis themselves as producing risk and, in some instances, even strengthen suspicions of a more direct or even causal role from cannabis exposure, particularly when prolonged. This generalization seems to hold especially regarding susceptibility to psychotic episodes and other emotional or cognitive adverse outcomes.

A major reason for the growing confidence in findings of negative health effects has been a series of changes affecting both the cannabis drug itself as currently marketed, as well as the power and subtlety of the research methods brought to bear on our understanding of the effects.

Simply put, the science has changed, growing more robust, as the drug and exposure to it has changed, the result being a more urgent sense of individual as well as population damage.

Specifically, the science informing our portrait of cannabis consequences has become more refined and more grounded in neurophysiology, as better techniques utilizing brain scans or animal models increasingly show what appear to be profound changes in brain physiology and function under certain circumstances of exposure.

In addition, wider and more careful evaluation of the consequences of *in utero* and perinatal exposure (as well as the potential impact of exposure of infants through maternal use and lactation) are all informing our understanding of the basis for epidemiological and behaviorally based evidence long seen with regards to the consequences of cannabis exposure.

That is, widespread population findings are now being provided with enhanced biologically based cognitive and neurophysiological reinforcement that the impact of cannabis consumption produces elevated behavioral and mental performance risks.

The drug as consumed likewise has changed from as recently as 20 years ago, not only with respect to average potency on the market (rising from roughly 3% THC to a national average of no less than 15% THC for smoked marijuana plant material), but further with respect to the relative market share of high potency product. Potency is not only rising as an average, but the proportions available in the commercial market are also shifting upwards towards higher potency smoked cannabis, such as found with sinsemilla, averaging nearly 20% potency, becoming the market standard.

Today, with respect to the "industrialized" ultra-high potency product accelerated by commercialization (still reportedly replete with heavy metal and fungal contaminates), we find available potencies routinely ranging from 20% THC to upwards of 40% as found in smoked joints filled with plant product, now supplemented by new products presenting concentrates of nearly pure THC (reported at 60–90% potency) capturing high-end commercial market share.

One corollary of these changes in potency is that longitudinal studies of youth, begun several years in the past, are therefore based on THC exposure at relatively low potencies, and as such their findings may not be reliably projected onto the impact that today's initiates may experience over their lifetime, given the far stronger doses that constitute their initiation experience.

That is, the marijuana of the past has been supplanted by a drug with qualitatively different characteristics and potential impact, with changes even found in shifting ratios of the cannabinoids presented (smaller percentages of CBD, for instance, diminished in favor of concentrated THC). Moreover, while there is evidence of some positive or at least ameliorative effect from CBD exposure, there are concerns that greater doses of CBD may produce biphasic responses. This potential

is only now being explored. Nevertheless, much of the modern commercial product has been deliberately selected for THC concentration at the expense of other cannabinoids, such as CBD.

Moreover, early blandishments from cannabis activists that such changes in the product, showing increasing potency of THC, were not "real" but were a function of measurement artifacts, or second if the changes were "real" that they need not signal greater ingestion of THC because users might titrate their dosages, or even arguments that stronger doses at higher potencies would not necessarily present greater risks of intoxication and potential dependency profiles, have all been shown to be illusory reassurances.

Instead, we have learned that users, especially naïve users, do not show a profile of careful titration, but instead seem to be getting dramatically more intoxicated, for longer periods than heretofore, coupled with growing evidence [1] that higher potency exposure is indeed correlated with increased risk of dependency or the onset of Cannabis Use Disorder (CUD).

Further, the modes of consumption of cannabis (principally THC) have changed, largely as a function of commercialization, generating not only new products but also new forms of their being consumed, such as in the form of edibles or drinks, or concentrated forms of the drug consumed no longer as smoked leaves but rather as forms of "shatter" or purified THC extraction products, often "vaporized" rather than smoked, or orally ingested.

One potential effect of such novel products is that our surveys of self-reported usage, especially by youth, are rendered less reliable as a measure of cannabis prevalence, since survey questionnaires built around models of smoked leaf consumption struggle to capture the proportions of consumption represented by the new modes of ingestion.

Increasingly, for instance, we learn that "edibles" [2] may now represent as much as half of new youth consumption, according to sales data from state dispensaries [3], while questions concerning "vaporizing" over and beyond "smoking" are only now being incorporated into standard youth surveys.

That is, the overall reliability of our measures of use is declining, and changes in the relative trajectory of youth use, in particular, are becoming less certain because of survey discontinuities (in particular, changes to the NSDUH survey methodology leading to a discontinuity with years prior to 2001).

The changes to the drug itself, and our means of detecting its effects, are intersecting with yet additional changes in the patterns of consumption, particularly by youth at developmentally susceptible periods. The window of susceptibility for developmental impact ranges from early adolescent exposure (not uncommonly at ages 12–15) up through early adulthood, at ages 18–25, when brain development still presents a vulnerability.

It should trouble us, for instance, that the age group showing the greatest increase in cannabis prevalence rates is the young adult population ages 18–25, as found in national surveys. Though subjects are in early adulthood, in terms of brain development they are still at a vulnerable period for negative cannabis effects to become long-standing adult problems.

Further, many of this age group live in a college or university setting, where nearly half of the student population is still legally underage for legal commercial purchase, comingling there with the young adults who are not only the heaviest users but are "legal" commercial product consumers. Do colleges present a particular domain of underage access to high-potency commercial cannabis acquired from peers?

Not only are more youth now exposed to cannabis markets as a function of state legalization and the rise of commercial markets, but the patterns of use are increasingly intensifying, in the sense that the frequency of use in youth populations is moving towards daily or near-daily exposure.

For instance, data from the largest national survey of drug use (discussed in detail below) show that the percentage of users of marijuana within the past year who used "more than 300 days" during the past year has risen steeply, from 12.2% of the total in 2002 to 19.8% of Past Year users in 2017, the most recent data available.

Hence, not only are more people using cannabis today than before, but they are using the drug more frequently, and at considerably higher potencies than before.

That is, a larger share of youth and young adult users, in particular, is gravitating towards a profile of use that presents the greatest developmental threat: frequent, repeated exposure at a developmentally sensitive period, an exposure that moreover is sustained for multiple years. The risk of developing Cannabis Use Disorder (CUD), for instance, becomes more pronounced with every year of use; according to recent research, for each succeeding year of exposure after initiation, the percentage of users experiencing CUD increases [4] steadily, rising to more than 20% of users at the fourth year of use beyond initiation.

As we have noted, longitudinal studies of the impact of early exposure traced over time into adulthood are worrisome enough, without taking into account that the THC potency routinely encountered at first exposure was likely a fraction of what an early adolescent is presented with today. This fact leads to the realization that the true developmental impact of early exposure, traced into maturity, is likely to understate the current potential impact, as the career of users initiating with high-potency THC products and then progressing to daily use at an early age has not yet been seen in current longitudinal studies.

In 1992, only 9% of Past Month cannabis users reported being heavy users (25 or more days per month). By 2014, that figure had risen to 40%. Recent analyses of dispensary users show that those "daily/near-daily" users consume about three times as much per day of use as less-frequent smokers and are estimated [5] to account for more than 80% of cannabis sales. Under the impact of high-potency THC consumption, tolerance progresses rapidly, and in order to sustain sufficient intoxication, dosages offered at unprecedented levels are now a routine share of all cannabis sales, and are escalating.

Hence, the damage that we observe today is best understood as a retrospective grasp of the consequences of cannabis exposure from a period when, in relative terms, the drug was less dangerous, while the impact of adolescent exposure today has as yet to be manifested, and is likely far worse than we have yet to witness. The

future may yet reveal a greater risk for early, frequent, high-potency use than we have anticipated.

These changing factors taken together will likely produce an enhanced understanding of the "disease burden" of greater cannabis prevalence following from "legal" commercialization, and resultant normalized attitudes towards ingestion in the wider society, and the likely correlative impact of heavy cannabis use on the use of other substances of abuse.

That "burden" may considerably exceed our current estimates, and even require us to rethink our sense of the "ranking" of drug threats, with vastly greater cannabis prevalence elevating substantially whatever impact is found at the individual level.

That is, this current experiment with cannabis, underway nationwide, is leading us towards a future of unanticipated consequences, a future already established in the patterns of use "seeded" in the population but as yet unmanifested.

To be sure, studies of cannabis risk are largely "correlational" or show "associations" with relative risk, and are not clear demonstrations of cannabis "causality," a rarity in any epidemiological undertaking.

Nevertheless, the correlations are compelling, especially when there is found a robust relative risk signal, a demonstration of a dose-response relationship between the exposure and the impact, and plausible biological pathways or mechanisms for the exposure to be linked to the effect, such as found in studies of brain development and in animal models.

Moreover, critics of the notion that cannabis exposure is causally linked to negative effects often fail to recognize that the "correlation" arguments constitute not just single dimensions of damaging effects, limited to one domain of biological consequences, but rather present a striking and wide-ranging "constellation" of studies and effects across a wide horizon of biological domains. What we increasingly see in research reports is a convergence of findings regarding cannabis risk that are mutually reinforcing.

That is, the dangers of exposure are found not only in brain physiology and function, ranging across a variety of functions and performances including cognition, memory, emotion, motivation, and potential psychological pathologies, but are further compounded by multiple behavioral studies and outcomes, involving school performance, lifetime achievement, susceptibility to social pathologies and disorders, and troubling propensities, such as suicide [6] risk.

In general, the literature shows not only multiple negative effects on large proportions of regular cannabis users, but we learn that for some specialized populations, such as those with mental or genetic predispositions or histories of pathologies or co-morbidities, cannabis exposure can be elevated beyond the risky to the level of the catastrophic, involving psychotic breaks and dissociations.

An added perversity is that many advocates, as well as those promoting greater commercial access and use of the drug, encourage exposure for populations already known to be at risk, such as sufferers of Post Traumatic Stress Disorder (PTSD), pregnant or nursing women, those with compromised immune systems, or those already at risk from substance use disorders, such as dependent opioid users.

That is, populations at high risk of developing cannabis abuse disorders and suffering disproportionately the consequences are being, perversely, targeted with messages to use cannabis as a putative protection or relief from their condition, either through so-called "medical marijuana" programs found in multiple states or through commercial, "recreational" market advertising and promotion. There are even direct targeted inducements [7] for pregnant women to consume marijuana to ease their afflictions, or unproven efforts to provide cannabis as an alternative to medications available for opioid use disorder, or even as a pain management regime thought to be superior to opioids.

In summary, each of these factors, when taken together, renders what dangers we thought were likely risks, as seen in the current literature, as being in fact likely understatements of the real risk now presented to the generation now affected, those coming of age in the era of a normalized, widespread, and aggressive market promoting drug exposure.

Limitations to Our Knowledge: Inadequate Measures, No Real Baseline

Before turning to current data showing the extent of cannabis use, it is important to stress the dismaying limitations on our knowledge. In some measure because drug use has been an illicit activity, our grasp of the true scope of prevalence, as well as accurate trajectories of change, has been deficient, perhaps presenting more uncertainty than found for any other large-scale medical challenge.

There are three major surveys providing information on use at the national level. The National Survey on Drug Use and Health (NSDUH), run under the auspices of the federal Department of Health and Human Services, is performed annually on a sample population of roughly 70,000 persons, with summed state-level data being reported every 2 years. The scope of coverage is taken to represent all Americans aged 12 and older living in households.

In addition, there are two surveys directed specifically at the youth/young adult population. Monitoring the Future (MTF) is conducted, under a grant from the National Institute on Drug Abuse (NIDA) to the University of Michigan, in select high schools (with a separate college age population segment), reporting on 8th, 10th, and 12th grade drug use. MTF routinely samples, on an annual basis, approximately 44,000 youth. The 12th grade data extend back to 1975, while the addition of 8th and 10th grade data begins since 1991.

The third is the Youth Risk Behavioral Survey (YRBS), overseen at the state level by the Centers for Disease Control (CDC). This survey is biennial, and questions a wide array of health-risk behaviors, only some of which behaviors include a substance use component. Prevalence rates are affected by the setting of the survey instrument, with school-based responses commonly exceeding those reported from households. Limitations on the YRBS as a national-level survey, (such as low response rates, incomplete state coverage, and even under-coverage

within states – the Colorado YRBS version has not had participation from the largest school district since 1995) render it less useful for our purposes.

None of the three surveys is an ideal surveillance instrument for a variety of reasons, the most prominent deficiency being that they all rely on self-reports of behavior, with the reports not subject to any objective evidence of actual exposure.

Moreover, the coverage of the sample populations presents an inherent limitation, given that either residence in stable households or current school attendance are necessary preconditions in order to be captured in the survey response. Hence, we may be systematically missing the very population most at risk for heavy substance use, since they may have suffered attrition from the sample population, being found neither in stable households nor enrolled in school.

While it is possible to supplement the findings of these surveys by reference to data such as drug-related arrests, incarcerations, treatment admissions, and hospital emergency department episodes, efforts to capture these data at the national level are inadequate, and poorly funded.

In fact, several sources of supplemental federal data on populations most at risk, such as the nationwide data-collections known as the Drug Abuse Warning Network (DAWN), which was focused on emergency department admissions (and/or mortality data), or the Arrestee Drug Abuse Monitoring (ADAM) program, focused on law enforcement intake populations, are currently unfunded at the national level, their operation suspended under the Obama administration.

Finally, though we can review the most recent survey reports (restricted in this discussion to the most reliable instruments, the NSDUH and the MTF), it remains a surprising fact that analysts at the federal level face considerable uncertainty establishing either the volume of illicit substances produced domestically or globally (Supply), and have even less reliable information on the volume of such substances consumed, or the market value of the products (Demand).

It follows that authorities trying to implement national drug control strategies that integrate “supply reduction programs” with “demand reduction programs” are faced with the reality that measurements of both supply and demand are woefully uncertain.

The challenge is particularly acute when it comes to cannabis production and consumption, since the metrics may rely on metric tons of organic material, while the most consequential variable should be the quantity of intoxicant actually consumed. Obviously, a marijuana plant with average THC potency of 3% available for market consumption is simply not comparable to a concentrated chemical product sold at 70% THC. Hence, the true metrics of actual THC consumption are exceedingly uncertain.

Current Measurements of Marijuana Use Showing the Comparative Scope of the Problem

Deficiencies aside, we can nevertheless observe relative changes over time in the self-reported data, even acknowledging that important populations with heavy use are likely not being measured at all.

American society has been plagued by various forms of substances of abuse throughout its history. But until the later half of the twentieth Century they did not include widespread consumption of cannabis, particularly by youth.

Before chronicling the most recent findings regarding cannabis use in the USA, as reflected in the 2018 National Survey on Drug Use and Health (NSDUH), it is worth a momentary reflection on the contemporary status of alcohol consumption as reflected by the same measuring instrument.

Surely some of the disease burden of a substance like alcohol is a function of its legal status for adults, producing prevalence rates of routine use that are multiples greater than the rates of use of cannabis, prior to legalization. If the impact of commercial legalization produces for cannabis prevalence rates in emerging generations that approach those of alcohol use, not only will cannabis use itself register as a more grave public health problem than it has been, its use somewhat truncated by legal risk, but the resultant impact of the concomitant use of alcohol and cannabis as dual public health threats could well exceed the damage of either of the substances taken alone.

That is, the future may present us with an intensifying "additive" model of substance misuse, as emerging and increasing cannabis patterns of use intersect with already prevalent alcohol use, there being little support for the hopeful speculation that cannabis use might supplant, rather than complement, concurrent alcohol consumption. Needless to say, measures of their interactive effects are as yet poorly developed.

A second reason to view contemporary alcohol consumption is that it might prefigure the potential scale of future cannabis consumption, after legalization and normalization of cannabis use becomes the context in which future generations acquire their norms of substance misuse.

Alcohol is more widely used, to be sure. But at least some of the disparity in prevalence is a function of the heretofore inhibitory effect on cannabis use deriving from the fact of societal prohibition, backed by legal sanction. Once those legal sanctions are removed, at least for adults 21 and older, we might be seeing in alcohol use the potential scale to which cannabis use might well grow, once promoted, fully commercialized, and normalized for a generation or more.

Accordingly, for the use of alcohol, in 2017, according to the NSDUH survey, there were in the population 12 and older 140.6 million current (Past Month) alcohol users, 66.6 million of which were "binge drinkers," 16.7 million of which were "heavy drinkers" during the Past Month, while 7.4 million drinkers were "under-aged."

While by no means inevitable, we see at least a plausible model for the scale of nationwide cannabis use following full legalization, a figure approaching fully half of the American population 12 and older routinely consuming an additional addictive substance.

Moreover, it would be a substance, cannabis, that has its greatest negative impact relatively early in life, compared to the worst negative health effects of alcohol, most commonly manifested later in life after years of abuse. In this regard one may further note recent research arguing that cannabis exposure is even more damaging [8] to adolescent brain development than is alcohol exposure.

To grasp the scale of illicit drug use, and its steep recent rise, we should look to what NSDUH terms Past Month (or "Current") use for the set substances identified as constituting use of "Any Illicit" drug (which category is inclusive of marijuana use).

Retrospectively, for 2015, shortly after early state-level commercial legalization of marijuana, NSDUH reported that during the course of that year, Past Month use of "Any Illicit" drug in the population 12 and older stood at 27.1 million Americans.

Scarcely a year later, however, the 2016 figures show a rise to 28.6 million users, an increase of 1.5 million additional drug users. This increase of Past Month users was nearly 6% in a single year.

The main reason for the overall "Any Illicit" increase can be found in the increased use of marijuana, which rose between 2015 and 2016 from 22.2 million Past Month marijuana users to 24 million users, an increase of 1.8 million users. The increase was just over 8%.

Since those data came out, NSDUH has advanced one more year to 2017 data (the survey results are released in September of the succeeding year, so the 2018 NSDUH report contains the 2017 data).

First, the new figures for "Any Illicit" drug use: In 2017, 30.5 million Americans 12 and older (that's about 1 in 9 Americans) were Past Month users of "Any Illicit" drug. That rise once again represents a slightly greater than 6% increase in a single year over 2016's 28.6 million users. That is, in two short years we have witnessed an increase in regular illicit drug use of 12%.

More specifically, focused just on marijuana, the 24 million Past Month users from 2016 has now risen to 26 million users in 2017. Again, for marijuana use, for the second consecutive year, the rise is just over 8% in a single year – yielding slightly greater than a 16% rise in what could arguably be seen as the first 2 years of the period post commercialization.

Marijuana use far outstrips the self-reported use of any other "illicit" substance.

The second-ranked "illicit" drug used is found in the misuse of prescription analgesics, with 3.2 million Current or Past Month misusers.

From there, the numbers drop even further, with the third-ranked drug, cocaine, having no more than 2.2 million Past Month users, while both methamphetamine and heroin both report fewer than 1 million Past Month users.

The contrast with marijuana use, the first-ranked illicit drug by far, is striking. While still lower than current use of alcohol, currently, the estimated 26 million Americans 12 and older reporting regular marijuana use in 2017 far exceeds any other substance use problem (leaving aside the issue of tobacco). The 26 million persons corresponds to 9.6% of the population 12 and older, and as we have seen, the figure is increasing by 8% with each passing year.

Where, then, is the population limit? What happens to our calculation of the relative "disease burden" of marijuana compared to alcohol when the number of users moves towards parity? Bear in mind that we are just now discovering the impact of legalization, which is still recent and partial across the states.

Moreover, the NSDUH survey allows the breakdown [9] of the population 12 and older into age groups, those 12–17, those 18–25, and those 26 and older. In addition to Past Month use, they also inquire as to Past Year use and Lifetime use.

Past Year use shows an enormous segment of the American population engaged in regular drug use. For Americans 12 and older, for 2017, there were 51.7 million Past Year users of any illicit drug. Of these, there were 40.9 million Past Year users of marijuana, or 15% of the population 12 and older. (By way of contrast, for the second and third leading illicit drugs, 6.6% misused psychotherapeutic drugs and 2.2% used cocaine.)

The increase since 2008, when there were 25 million Past Year marijuana users, is a stunning 64%. The percentage of users for 2017 exceeds any year, based on data that track back to 2002, before which year the survey was rendered discontinuous because of changes in methodology. The increase is driven most by those aged 18–25 and by those 26 and older. In 2017, among those aged 18–25, Past Year use of marijuana stood at 11.9 million (34.9% of this age group).

Switching categories now to the more regular Past Month users, how are the drug usage patterns distributed? Of adolescents, 12–17 years old (those arguably most at risk for damage), 6.5% were Past Month (Current Users) of marijuana. That figure represents approximately 1.6 million adolescents.

For 18–25 year olds, 22.1% (more than 1 in 5) were Past Month marijuana users. The figure has risen in a statistically significant manner every year since 2012, when it stood at 18.7%. That figure represents about 7.6 million young adults.

For adults 26 and older, the percentage for Past Month marijuana use is 7.9%, nearly double of what it was in 2008 at 4.2%. The current percentage represents about 16.8 million adult Past Month marijuana users.

Summarized 2017 Findings in Brief Tabular Form for Past Month and Past Year Marijuana Use:

- NSDUH 2017 [10] (reported in 2018): among approximately 70,000 people 12 and older surveyed:

- Past Year Marijuana Use ages 12–17: 12.4%
- Past Month Marijuana Use ages 12–17: 6.5%

- Past Year Marijuana Use ages 18 and older: 15.3%
- Past Month Marijuana Use ages 18 and older: 9.9%

- Past Year Marijuana Use ages 18–25: 34.9% (the increase from 2007, which showed 27.5% using, is 27%)
- Past Month Marijuana Use ages 18–25: 22.1% (the increase from 2007, which showed 16.5% using, is 34%)

- Past Year Marijuana Use ages 26 and older: 12.2% (the increase from 2007, which showed 6.8%, is 79%)
- Past Month Marijuana Use ages 26 and older: 7.9% (the increase from 2007, which showed 3.9%, is 102%)

In addition to overall increases in prevalence, we also see the "intensification" of use patterns. For all ages 12 and older, among Past Year users, the percentage of "daily/near daily" marijuana use stands at 19.8%, and at 21.9% for those 18–25.

Among Past Month marijuana users 12 and older, the average number of days used during the past month is 14.5 days, while the percentage of Past Month users consuming marijuana "daily/near daily" is a remarkable 41.7%. (NSDUH [11] table 7.21 B).

For those Past Month users who are aged 12–17, 25.1% were "daily/near daily" users.

For the 22.1% of those aged 18–25 who are Past Month users, the "daily/near daily" percentage stood at 44.3%.

Use of marijuana on a "daily/near daily" basis is the pattern of exposure most likely to produce Marijuana Use Disorder (the term for Cannabis Use Disorder or CUD). For 2017, CUD in the Past Year was reported as 5.2% for the category of 18–25 year olds.

Cannabis Use Disorder (CUD) is rising, in general. Data [12] from the National Epidemiology Survey on Alcohol and Related Conditions (NESARC), comparing successive waves of data between the years 2001–2002 and the years 2012–2013, show that the prevalence of marijuana use more than doubled, which prevalence was accompanied by a large increase in CUD experienced within the past year, largely because of the increase in the number of users.

According to NESARC, nearly 3 in 10 marijuana users experienced CUD. (The rate of CUD among marijuana users, however, did not increase, potentially owing to the fact that the "pool" of new users may have dampened the overall rate of disorder; subsequent NESARC waves, especially given the steeply rising potencies now experienced, may disambiguate the factors behind changes in CUD rates.)

Moreover, based on the same survey data set, additional research [13] has shown that the increase in CUD prevalence was greater in states that had passed "medical marijuana" laws than in states that had not.

Marijuana Use in Sub-populations at High Risk

Even further insight [14] regarding our future threat can be seen in use of marijuana by specialized populations presenting particular risks.

For pregnant women, aged 15–44, 7.1% report using marijuana during the Past Month. This represents an increase since 2015, when it stood at 3.4%, of 108% in two years. On the whole 3.1% of pregnant women report "daily/near daily" marijuana use, up from 1.2% in 2015.

For youth aged 12–17 who are Past Year "daily/near daily" marijuana users, 15.5% report a co-morbidity of past month "heavy alcohol use" while 24.1% report a Major Depressive Episode (MDE).

On the whole 31.8% of Past Year "daily/near daily" marijuana users suffer a co-morbidity of past-year opioid misuse (reported by only 1.6% of non-marijuana users for this co-morbidity).

The corresponding figures for the age group 18–25, by Past Year "daily/near daily" marijuana use, are: 20.7% Heavy Alcohol Use, 17% past year Major Depressive Episode, and 24.1% past year Opioid Use Disorder, respectively, for the co-morbidities reported.

Monitoring the Future School-Based Data

Some additional insights on the scope of youth exposure can be gained from the Monitoring the Future Survey of high-school youth. MTF 2018 [15] is a school-based survey reporting on 44,482 students from 392 public and private schools, examining self-reported substance use amongst 8th, 10th, and 12th graders (as mentioned earlier, the trajectory for 8th and 10th grades begins since 1991, while reports from 12th graders have been gathered since 1975).

For 12th graders, 22% report Current, or Past Month, marijuana use (a rate that exceeds cigarette use, which has fallen to 7.6%; binge drinking, at 13.8%, has been in steady decline since 1998). Past Year marijuana use stands at 36.9%.

Of current enrolled students, 5.8% of 12th graders report daily marijuana use.

In a troubling recent development, 37% of 12th graders report vaping some substance, primarily nicotine, while the 13.1% report vaping marijuana or hash oil. The rise between 2017 (the first year that inquired about vaping) and 2018 for all grades reporting vaping marijuana is significant (for 8th and 10th graders, it is 63%).

For vaping marijuana (only), the rise for 12th graders is from 4.9% in 2017 to 7.5% in 2018, an increase of 53% in a single year.

It may well be that we are failing to capture the full extent of marijuana use prevalence because of the rise of vaping and consumption of comestible forms of the drug are only now being systematically included in the survey instruments.

Additionally, MTF [16] reports that marijuana use among college age students, seen among a cohort that they track beyond high school, has risen steeply. They report that 30-day use of marijuana has increased significantly by 5.1% across the past 5 years, ending in 2018 at 24.1%, an all-time high for the study. In fact, annual and 30-day marijuana use among young adults aged 19–28 are at the highest levels in the 33 years that MTF has been monitoring their use.

Finally, MTF has for years measured subjective norms regarding the acceptability of smoking marijuana, as well as asked concerning student perceptions [17] of risk in using. These two metrics are often seen as harbingers of future prevalence; for instance, when perceptions of risk rise, prevalence rates tend to fall shortly after. Disturbingly, therefore, we learn from the most recent MTF perceptions by high school seniors of harmfulness in regular use of marijuana have fallen from high of 78.6% in 1991 to only 26.7% in 2018, a fact which may well show the triumph of the misleading “medical marijuana” campaign.

Widening Societal Impact of Increased Marijuana Prevalence

It is disturbing to realize that no one knows the full societal impact of these kinds of drug use changes spreading into every sector of the nation. Surely we can expect some societal consequences, not least on educational attainment, on workforce performance, on economic attainment, and even military recruitment, over and above the consequences found in strictly public health or criminal justice dimensions.

A recent (and proprietary) publication from Baron Public Affairs, a risk-assessment firm that provides analysis and guidance to public policy and corporate

decision makers, evaluated the possible impact of commercial marijuana in a document entitled "The Unintended Consequences of Marijuana Legalization."

While by no means exhaustive, their research nevertheless identified several areas of societal concern over the emerging levels of marijuana use, which concerns extend beyond just the public health and criminal justice impact.

The Baron report anticipated widespread impact on individual initiative and motivation, affecting the economic prospects not only for the generation of heavy users but for the wider economy. They noted such effects as those who smoked marijuana regularly had lower social class as adults than their parents experienced. They also had greater levels of welfare dependency and higher levels of unemployment.

Given further effects, such as those on family formation and collapsing social capital, Baron anticipated even greater social stratification, income inequality, greater damage to those with fewer economic resources, and greater class conflict.

Baron further anticipated a link to the multi-billion dollar opioid crisis, to which the coming marijuana epidemic will add further addiction and greater need for government services, welfare relief, and public funding, particularly for treatment purposes, to address the consequences of widespread marijuana use.

To these effects they add alarms concerning the available pool of warfighters and the potential erosion of military standards through either drug use waivers or tolerance of on-going use, which could render users compromised as decision-makers and vulnerable as security risks.

Even after the acute effects of intoxication have faded, users may experience reduced [18] cognitive/executive function, long-term, with strongest effect on adolescents.[19]

Finally, with regards to economic impacts, Baron notes that in one rural area, half of all job applicants were reported to have failed their employment drug test, which in a tight labor market is an obstacle to growth. In fact, data [20] from the largest national drug testing business, Quest, show that those who fail an employment drug test stands at its highest level (4.4% in 2018) in 14 years.

We are only at the beginning of the consequences of commercialization. The recent political calculus of both California and Canada to enter commercial marijuana markets has during the last 2 years added a combined population of nearly 77 million persons now living under "legal" marijuana regimes.

No wonder, as Baron concludes, has cannabis investment nearly quadrupled during the year 2018, built on major investments from well-established tobacco, pharmaceutical, and alcohol companies.

The Societal Impact of Expanded Cannabis Extends to the Use of Other Substances Of Abuse

First, we should recognize that trafficking networks for all drugs penetrate expanding marijuana markets. These criminal networks operate with a business model that is polydrug and polyfinance, operating with violence, coercion, and corruption as standard modes of behavior, capitalizing on addiction.

There are multiple ways in which the spread of marijuana prevalence is tied to the continued strengthening [21] of the illicit criminal market not only for marijuana but also for the trafficking in all illicit drugs, including the opioids.

Criminal organizations are polydrug traffickers, and wherever they establish a presence by capitalizing on the expanding commercial prevalence of marijuana, they begin to exploit their access to traffic other substances, thereby feeding [22] not only the opioid crisis (responsible for 47,000 of the overall 70,000 overdose deaths from all drugs in 2017) but further fueling the overdose crisis in cocaine (deaths rising rapidly to over 13,000 in 2017) and methamphetamine (contributing to over 10,000 deaths nationwide in that same year).

To take but one example, in Colorado [23], between 2015 and 2016, after steady rise since 2002, pharmaceutical opioid overdose deaths declined by 6%. But in that same year, overdoses from heroin increased 23% (subsequent data have shown that even the pharmaceutical overdose deaths have rebounded upward). Numerous communities, such as Pueblo, note that rapid expansion of homeless populations following the proliferation of marijuana dispensaries has been accompanied by increased trafficking and use of methamphetamine, illicit opioids, and cocaine, the effects of which can be observed in local emergency rooms.

Moreover, the financial profits accruing to the criminal cartels from marijuana sales serve to fund the full scope of their trafficking activities, supporting their capacity to insulate themselves not only financially but also politically.

To understand the broader relationship between adolescent drug use, including the initiation of marijuana, and the persistence of our current opioid overdose epidemic, we can turn to the work of Dr. Robert DuPont, a psychiatrist who is President of the Institute on Behavior and Health.

DuPont recently authored [24] *"A New Narrative to Understand the Opioid Epidemic,"* noting that for many opioid-addicted individuals, drug use frequently began in early adolescence, particularly with the use of alcohol and marijuana. "Early poly-drug use often sets the stage for later transition from medical to addictive use of opioids that are prescribed for pain. These patients' brains have been primed for the addictive response to opioids."

As DuPont notes, opioid overdose deaths nearly always involve the use of other addictive drugs, such as marijuana, cocaine, methamphetamine, and alcohol. About 95% of current opioid overdose deaths, according to studies of particular populations, involve other drugs, with an average of 2–4 and a maximum of 11 in addition to the opioids.

The standard overdose narrative, DuPont argues, overstates the degree to which physician prescribing of opioid medications is the primary pathway for overdose risk and ignores the significant role of adolescent initiation to drug use in the opioid overdose epidemic, occurring at older ages. While for many opioid addicted people their first use of an opioid was a prescribed opioid from a physician, it is also true that the majority of these individuals first used other drugs before or with their first use of opioids.

Further, only about 4% of people who use prescription opioids non-medically initiate heroin within 5 years of first prescription opioid use. For example, among 4493 individuals treated for opioid addiction whose first exposure to opioids was through a

prescription from their physician, notably 94.6% reported prior or coincident use of other psychoactive drugs. Alcohol was used by 92.9%, and marijuana by 87.4%, and excluding these top substances, fully 70.1% reported other prior or coincident drug use.

The clear message is that in order to comprehensively address the current drug abuse crisis and accompanying fatalities, we must address early adolescent exposure to marijuana as a contributing factor.

Multiple accounts now found in the literature clearly show that cannabis use, especially persistent use of high-potency cannabis in adolescence, is a risk [25] factor for the development of subsequent opioid use disorder.

To take but one example, a 2017 study [26] using NESARC data found specifically that cannabis use is linked to prescription opioid disorder: "… cannabis use at wave 1 was associated with increased incident nonmedical prescription opioid use (odds ratio = 5.78) and opioid use disorder (odds ratio = 7.76) at wave 2."

As the Centers for Disease Control succinctly summarized [27] the matter, "People addicted to marijuana are three times more likely to be addicted to heroin." In addition, multiple studies, particularly using animal [28] models, show an effect of brain "priming" and "cross-sensitization" between cannabis exposure and opioid exposure. Overall, we are witnessing increasing validation of a marijuana "gateway" [29] effect on subsequent drug use. Indeed, there is increasing evidence [30] that "early marijuana use by itself, even after control for other covariates, increases [31] significantly the use of other illicit drugs."

Final Thoughts on the Wider Implications of Increased Use

The full scope of the potential negative effects of increased marijuana use, particularly as accelerated by commercial legalization, is now emerging, and the damage affects many domains of national life.

First, we should be concerned over the future impact of a marijuana "gateway" effect, whereby early adolescent exposure increases the risk of subsequent initiation of other addictive substances, and further heightens the risk of multiple drug use disorders in later life.

To the extent that the gateway thesis is validated, we can expect that the surging crisis in the use of drugs such as opioids, cocaine, methamphetamine, and other emerging synthetic drug threats will continue at an epidemic level, as widespread marijuana prevalence serves to feed vulnerable users into polydrug dependency and disorders.

Moreover, it is not just the users of such substances who are placed at risk, we recognize that major criminal enterprises, those that traffic lethal poisons, find in the "legal" marijuana market an open pathway for their operation, thereby enhancing their revenue, and reinforcing their violent and corrupting methods.

But the public health impact is not limited to the effect on users. We should acknowledge that the rise of "medical marijuana" treated as though it were a legitimate medicine approved through clinical trials, scientific rigor, and demonstrations

of safety and therapeutic efficacy, shows the consequence of allowing a political process to supplant strict medical trials as the basis for legal acceptance.

As such, the integrity of the drug approval process itself, and the authority of the criteria upon which it is based, has been compromised by resort to illegitimate mechanisms.

Further, there are lessons to be learnt in how both "medical" and commercial marijuana progressed at the state level, in settings such as Colorado. Promises were made by advocates, seeking a political appeal to sway voter approval. Promises were made of enhanced state revenue sufficient to compensate for possible public health or law enforcement costs. Promises were made of more effective means for protecting youth from access to the drug. Promises were made of forcing out criminal activity, with its attendant violence, coercion, and fear. Promises were made of reducing supposed injustices in legal enforcement of anti-drug laws.

In fact, so appealing were the promises that the Obama administration's Department of Justice (DOJ) agreed to reorder federal prosecutorial priorities to enable state legislation to operate. In repeated memos from the DOJ we were told that there would be established certain "Red Lines," which, if crossed, would trigger an intervention on behalf of federal law. The "Red Lines" pertained to such issues as drug access by youth, or evidence of smuggling activities, or other signs of criminal activity.

Yet we cannot forget that those "Red Lines" were repeatedly, even flagrantly, violated in succeeding years, as multiple reports from the Rocky Mountain High Intensity Drug Trafficking Area (HIDTA) [32] joint law enforcement command readily demonstrated. But no federal intervention was triggered. (Further, we now see evidence at the state level that the promised taxation revenue has not been sufficient to cover the greater costs to society of increased prevalence, nor have certain putative benefits manifested, and that black market marijuana, offered more cheaply, has captured major market share.)

Suffice it to say that the promises have not been kept. Yet we now see them repeated at the national level.

So as we pull back the lens for a wider picture, we see not only a public health crisis affecting users and medical institutions, but an emerging criminal justice crisis, as the black market thrives in states that have approved commercial marijuana, and as violence, smuggling, and corruption have all persisted in support of strengthened criminal activity, which now seeks to insulate itself by gaining political [33] power.

As noted, there are now efforts in Congress to alter at the federal level not only the Schedule I status of marijuana but further enable banking and financial legislation that could threaten the integrity of the US financial system, were transnational criminal organizations could exploit the proposed changes to mask or launder illicit proceeds from their entire international operations.

If we pull the lens back even further, we now see the international impact of our failure to uphold federal drug law at the state level. Simply put, the position of the USA as the moral leader in drug control, and the primary protector of the global drug control enterprise, has been compromised.

Our international commitments, such as found in treaty obligations in partnership with the United Nations, have been countermanded. Our allies, themselves fighting transnational criminal organization, feel abandoned, and many are yielding the fight. Even US development objectives, seeking to strengthen not only international economies but human rights and democratic institutions, have been eroded by the threatened emergence of corrupt narco-states among international partner nations who once depended on us for protection.

That is, we can now count the costs of the spreading acceptance of legalized drug use as serving to damage not only public health and criminal justice, but national security as well.

None of these developments make our own borders more secure, nor our own citizens safer nor healthier. In fact, US interests and well-being may be facing a coming debacle of major dimensions through unprecedented drug use and the attending criminal attack on our institutions, financial as well as political.

It should finally trouble us greatly that all of these developments represent self-inflicted wounds, against which many have warned us. We may well find that we done no other than to enable a virtual Trojan Horse in our midst, a development likely to occasion great regret.

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