SB 113 Problems with Marijuana as a Medicine

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Chairman Suellentrop, as a practicing physician and also an internationally recognized expert on marijuana, I am opposed to SB113. It is further disingenuous to call this the "Veterans" bill when marijuana actually has negative effects on PTSD sufferers and results in more violent episodes (article attached).

To put this issue in perspective, I cannot imagine that this esteemed committee would be considering medicinal applications of cigarettes if it were being proposed by the tobacco lobby and its apologists. Why then do we even begin to consider smoking pot for medical uses? Pot is essentially tobacco with the intoxicant THC as well as cannabinoids including THC and CBD both of which are now commercially available.

It is poor medical practice to have medical substances approved by legislation rather than by the scientific processes involved in FDA approval. Substances that are used for medicinal purposes need to either go through the rigorous process of FDA approval, or they need to be part of an approved research program. **Street smoked pot does not under any circumstances constitute medicine.** Furthermore, while several other states have caved in to special interest pro-marijuana lobbying efforts, Kansas needs to stand strong and push back against this movement.

I have provided recent medical summaries of the marijuana issue that have concluded marijuana availability by legislation is simply not the way to proceed and have questioned medicinal use of marijuana. The most recent was published in JAMA, the Journal of the American Medical Association, a couple weeks ago.

Addition considerations:
1) Marijuana is smoked. There are no other medicines that are smoked and that knowingly expose users to toxic harmful chemicals.

2) The potentially therapeutic substances that exist in marijuana are either commercially available or soon to be available as pure and standardized medicine.

3) Dangerous impurities and contaminants have been regularly identified in marijuana smoke. (See attached article)

4) Marijuana and the cannabinoids have not been shown to consistently be therapeutically effective medicine.
*AnnInternMed.* doi:10.7326/M17-0155 **Conclusion:** Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.

5) Marijuana abuse among adolescents is higher in states that have allowed medical uses.
*JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2017.0724 Published online April 26, 2017.

Tucker, J.S., Rodriguez, A., Pederson, E.R., et al. (2018). Greater Risk for Frequent Marijuana Use and Problems Among Young Adult Marijuana Users with a Medical Marijuana Card. *Drug and Alcohol Dependence*. doi.org/10.1016/j.drugalcdep.2018.09.028

6) Marijuana use has now been linked to domestic and dating violence as well as general violent behavior.
Miller and Oberbarnscheidt, J Addict Res Ther 2017, S11:014 DOI: 10.4172/2155-6105.1000S11-014
Journal of Interpersonal Violence 25(6) 1043–1063 © The Author(s) 2010 Reprints and permission: http://www.sagepub.com/journals Permissions.nav DOI: 10.1177/0886260509340543 http://jiv.sagepub.com

7) A new infrastructure would be necessary to monitor marijuana.

8) Psychiatric complications and destabilization of psychiatric patients would increase

9) Marijuana has been proposed as a substitute for Opiates. In fact, use of marijuana is associated with **increased Opiate use** and is considered by experts to be inappropriate.
Humphreys K, Saltz R. JAMA 2019 Vol 321

10) Trials of marijuana for PTSD have actually demonstrated more violence and drug use in the marijuana trial groups (article included)

NBC News 3/23/15
This is not your father's weed.
Colorado marijuana is nearly twice as potent as illegal pot of past decades, and some modern cannabis packs triple the punch of vintage ganja, lab tests reveal for the first time.
In old-school dope, levels of THC — the psychoactive chemical that makes people high — were typically well below 10 percent. But in Colorado's legal bud, the average THC level is 18.7 percent, and some retail pot contains 30 percent THC or more, according to research released Monday.
"That was higher than expected," said Andy LaFrate, president of Charas Scientific. His Denver lab is licensed by the state and paid by marijuana businesses to measure the THC strength in their products before they go to market. "It's common to see samples in the high 20s."
**How the pros make legal marijuana**
CNBC

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What's really in — and not in — Colorado's retail weed surprised LaFrate. After analyzing more than 600 samples of bud provided by certified growers and sellers, LaFrate said he detected little medical value and lots of contamination. He presents those

findings Monday to a national meeting of the American Chemical Society, a nonprofit scientific group chartered by Congress.
"We don't want to be alarmists and freak people out, but at the same time we have been finding some really dirty marijuana," LaFrate told NBC News.
Some green buds he viewed were covered in funghi — and he estimated that several marijuana flowers were "crawling" with up to 1 million fungal spores.
"It's a natural product. There's going to be microbial growth on it no matter what you do," LaFrate said. "So the questions become: What's a safe threshold? And which contaminants do we need to be concerned about?"
For example, he also examined more than 200 pot extracts or "concentrates" and found some contained solvents like butane. All the tests were done with high-performance liquid chromatography, a method to separate, classify and measure individual compounds.
What LaFrate didn't see, however, also astonished him. The 600-plus weed samples generally carried little or no cannabidiol, or CBD — the compound that makes medical marijuana "medical." The average CBD amount: 0.1 percent, his study reports.
CBD is anecdotally known to control depression, anxiety, and pain. About 200 families with ill children also moved to Colorado to access a strain called Charlotte's Web, which appears to control seizures in some kids.

"It's disturbing to me because there are people out there who think they're giving their kids Charlotte's Web. And you could be giving them no CBD — or even worse, you could be giving them a THC-rich product which might actually increase seizures," LaFrate said. "So, it's pretty scary on the medical side."

The majority of samples tested came from recreational-pot merchants. Under Colorado law, recreational weed must be tested for potency. Some medical-pot sellers voluntarily provided samples to LaFrate. Colorado does not require pre-sale testing of medical marijuana. LaFrate did not analyze any edibles.
"Really, there is very little difference between recreational and medical in terms of the THC-to-CBD ratio, at least at the aggregate level," LaFrate said.
What does that mean for buyers? There may be little difference in how various strains make users feel, even though some people claim one type induces relaxation and another hikes alertness, LaFrate said.
Three decades of cross-breeding pot strains — done to meet a demand for stronger weed — generally elevated THC and decreased CBD in many ways is not your father's weed. Colorado marijuana is nearly twice as potent as illegal pot of past decades, and some modern cannabis packs triple the punch of vintage ganja, lab tests reveal for the first time.
"These samples are representational, I think, of what's happening here in the state and, probably, across the country," LaFrate said. "Because most of the new states coming online with medical or retail marijuana have people from Colorado coming in to set up those markets.
Azzariti also champions contamination testing as "an integral part of our industry."
"I personally am very excited to see technology in testing continue to advance. You would be very hard pressed to find a garden that hasn't at one point had some sort of

issue, whether it's an infestation, microbial problems," said Azzariti, an Iraq War veteran. He uses cannabis to help treat post-traumatic stress disorder.

On Jan. 1, 2014, he became Colorado's first buyer of legal weed.

Meanwhile, pot-legalization opponents are using LaFrate's findings to compare retail weed to food raised or grown with genetically modified organisms or GMOs. And pot foes continue to link the rise of the marijuana industry to the long-ago advance of Big Tobacco.

"This study is further evidence that Colorado legalization is not working. It proves that even under government control, there's no way to ensure marijuana is free of bacteria and chemicals," said Kevin Sabet, president of Smart Approaches to Marijuana (SAM). "This shows that marijuana is a GMO product just like other products sold by big business. And just like other industries, now you have a big marijuana industry determined to hide these findings from the public. Where is their outcry? Where are the promises to change the way they do business?" Sabet said. "I won't hold my breath. For years, the tobacco industry did the same thing. Welcome, America, to Big Tobacco 2.0 — Big Pot."

EDITORIAL



# Medical Marijuana
## Is the Cart Before the Horse?

Deepak Cyril D'Souza, MBBS, MD; Mohini Ranganathan, MD

**There is a pressing need** to develop new medications for many debilitating conditions. Novel approaches based on marijuana or its constituent cannabinoids, if proven, could be added to the armamentarium of available treatments. In this issue of *JAMA*, reviews by Whiting et al[1] and Hill[2] provide detailed assessment of the pharmacology, indications, benefits, adverse effects, and laws related to medical marijuana and the cannabinoids, and the results and conclusions are consistent. There is some evidence to support the use of marijuana for nausea and vomiting related to chemotherapy, specific pain syndromes, and spasticity from multiple sclerosis. However, for most other indications that qualify by state law for use of medical marijuana, such as hepatitis C, Crohn disease, Parkinson disease, or Tourette syndrome, the evidence supporting its use is of poor quality. State laws vary widely regarding conditions for which marijuana is approved and the dispensable legal limit. Both reviews raise important issues worthy of further discussion.

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First, for most qualifying conditions, approval has relied on low-quality scientific evidence, anecdotal reports, individual testimonials, legislative initiatives, and public opinion. Imagine if other drugs were approved through a similar approach. The US Food and Drug Administration (FDA) requires evidence from at least 2 adequately powered randomized clinical trials before approving a drug for any specific indication. For most of the conditions that qualify for medical marijuana use, the evidence fails to meet FDA standards. It has been argued that the lack of high-quality evidence reflects the difficulty in conducting marijuana research in the United States. If so, the federal and state governments should support and encourage such research so that high-quality evidence can be generated to guide decisions about medical marijuana use for the conditions for which the existing evidence is either insufficient or of poor quality.

Second, there are inconsistencies in how medical conditions are qualified for medical marijuana use within a state and between states. For example, in Connecticut, psoriasis and sickle cell disease but not Tourette syndrome qualify, even though the supporting evidence for all 3 conditions is uniformly of very low quality. Similarly, posttraumatic stress disorder (PTSD) is approved as a qualifying condition in some but not all US states. These differences reflect inconsistencies in evaluating and applying current evidence toward decision making about qualifying indications for medical marijuana use.

Third, unlike most FDA-approved drugs that typically have 1 or 2 active constituents, marijuana is a complex of more than 400 compounds including flavonoids and terpenoids and approximately 70 cannabinoids other than $\Delta^9$-tetrahydrocannabinol (THC)[3]. These cannabinoids have individual, interactive, and even entourage effects (effects of a compound that are only appreciable in the presence of other compounds) that are not fully understood and that contribute to the net effect of marijuana. Although clinical trials for some of the qualifying conditions and studies in animal models of those conditions have been conducted with individual cannabinoids (eg, THC or cannabidiol [CBD]), given that marijuana has so many constituents, the results of studies with individual cannabinoids (eg, THC or CBD) cannot be extrapolated to marijuana and vice versa. In addition, unlike FDA-approved medications that have a relatively uniform composition, the composition of cannabis preparations can vary substantially in its content of THC and CBD, such that precise dosing may be difficult. Given the variable composition, patients will have to experiment with different strains and doses to achieve the desired effects, without much input or oversight by physicians.

Fourth, some individual cannabinoids are already commercially available in the form of dronabinol and nabilone. These drugs are administered orally, and some published data are available to guide dosing. In contrast, there are few data on dosing smoked medical marijuana for many of the qualifying medical conditions for which it is used.

Fifth, while the acute adverse effects of marijuana are quite well known, the effects of repeated exposure, as would occur with medical marijuana, need further study. Approximately 1 in 10 adult users of marijuana develops addiction, and this number is even higher among adolescents.[4] Tolerance and dependence with accompanying down-regulation and desensitization of type 1 cannabinoid receptors occur with repeated exposure.[5] Based on this profile, marijuana dosing will have to be increased over time to achieve the same effect. A distinct withdrawal syndrome is also well recognized.

There is also a small but definite risk of psychotic disorder associated with marijuana use, as well as a significant risk of symptom exacerbations and relapse in patients with an established psychotic disorder.[6] Thus, explicit contraindications such as schizophrenia, bipolar disorder, or substance dependence need to be identified along with measures to minimize the likelihood that persons with contraindications would be able to obtain medical marijuana. Perhaps US states should establish clinical follow-up programs to monitor long-term outcomes prospectively, especially negative outcomes (eg, new cases of psychosis) in patients with contraindications.

Sixth, the interactions of marijuana with other drugs that may be concurrently prescribed for qualifying conditions need further study. There are claims that medical marijuana may allow patients to lower their opioid analgesic doses. However, the existing evidence does not support this contention.[7,8] Furthermore, there is some evidence of cross-tolerance between cannabinoids and opioids[9] that should be considered in attempting to partially or fully substitute opioids with marijuana in the treatment of pain syndromes. Perhaps medical marijuana should also be included in monitoring databases as has been done for opioids and benzodiazepines, so physicians could have a more complete understanding of the medication profile of their patients.

Seventh, emerging evidence suggests that the endocannabinoid system is critical in brain development and maturational processes, especially during adolescence and early adulthood. The endocannabinoid system is involved in axon elongation, neurogenesis, neural maturation and specification, glia formation, neuronal migration, and synaptic pruning.[10,11] Furthermore, the endocannabinoid system evolves during adolescence.[12] Unlike endocannabinoids, which have short durations of action, exposure to exocannabinoids (present in marijuana [eg, THC]) activates the endocannabinoid system in a prolonged nonphysiological manner. In preclinical studies, adolescent exposure to cannabinoids has been linked to long-lasting alterations in the endocannabinoid system, as well as other neurotransmitter systems.[13] Collectively, these changes in the endocannabinoid system have been linked to affective, behavioral, cognitive, and neurochemical consequences that last into adulthood. Data on the effects of repeated exposure to marijuana among youth must necessarily rely on epidemiological studies, which thus far support the animal data in demonstrating long-term consequences including cognitive deficits and increased risk for psychosis. Careful consideration is needed to determine at what age exposure to medical marijuana is justifiable because of the following factors: (1) brain development continues until age 25 years; (2) the endocannabinoid system is involved in brain development; and (3) cannabinoid exposure during critical periods of brain development is associated with long-lasting changes in behavior and cognition.

Eighth, it is important to understand the mechanism(s) underlying the potential beneficial effects of marijuana or its constituent cannabinoids. Specifically, it is uncertain how or why marijuana could be effective in treating epilepsy, sickle cell disease, PTSD, Crohn disease, psoriasis, or amyotrophic lateral sclerosis—conditions with no obvious common pathophysiology. Perhaps marijuana provides nonspecific subjective relief, similar to the effects of benzodiazepines.

For physicians, the legal implications of certifying patients for medical marijuana remain unclear given the differences between the views of state vs federal government. Marijuana is classified as a Schedule I substance by the FDA, meaning it has no currently accepted medical use and a high potential for abuse from a federal perspective. The prescription, supply, or sale of marijuana is illegal by federal law. Furthermore, it is not known to what extent, if any, a physician who certifies a patient for medical marijuana may be liable for negative outcomes (eg, motor vehicle crashes). It is not known if malpractice insurance will cover liability attributable to physicians certifying medical marijuana use.

In conclusion, if the states' initiative to legalize medical marijuana is merely a veiled step toward allowing access to recreational marijuana, then the medical community should be left out of the process, and instead marijuana should be decriminalized. Conversely, if the goal is to make marijuana available for medical purposes, then it is unclear why the approval process should be different from that used for other medications. Evidence justifying marijuana use for various medical conditions will require the conduct of adequately powered, double-blind, randomized, placebo/active controlled clinical trials to test its short- and long-term efficacy and safety. The federal government and states should support medical marijuana research. Since medical marijuana is not a life-saving intervention, it may be prudent to wait before widely adopting its use until high-quality evidence is available to guide the development of a rational approval process. Perhaps it is time to place the horse back in front of the cart.

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VIEWPOINT

# Should Physicians Recommend Replacing Opioids With Cannabis?

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**Recent state regulations** (eg, 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.

## Efficacy of Cannabis for Chronic Pain and for Opioid Use Disorder

Recent systematic reviews[1,2] 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 (eg, 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 review[3]).

> In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.

The evidence that cannabis is an efficacious treatment for opioid use disorder is even weaker. To date, no prospective evidence, either from clinical trials or observational studies, has demonstrated any benefit of treating patients who have opioid addiction with cannabis.

## Comparative Effectiveness: Substituting Cannabis for Opioids

Substituting cannabis for opioids is not the same as initiating opioid therapy. There are no randomized clinical trials of substituting cannabis for opioids in patients taking or misusing opioids for treatment of pain, or in patients with opioid addiction treated with methadone or buprenorphine. In addition to surveys of patients who use medical cannabis, the other types of studies prompting a move to cannabis to replace opioids are population-level reports stating that laws allowing medical cannabis use are followed by fewer opioid overdose deaths than expected. 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 (eg, between medical cannabis and opioid overdose) may be opposite of those seen within individuals. In the only individual-level analysis, which included 57 146 people aged 12 and older, of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.[4]

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.[5] 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.

For opioid use disorder, there is concern that the New York State Health Commissioner has defined opioid addiction to include people being treated with US Food and Drug Administration–approved, efficacious, opioid agonist medications, as a qualifying condition for medical cannabis.[6] Methadone and buprenorphine treatment reduces illicit opioid use, blood-borne disease transmission, criminal activity, adverse birth outcomes, and mortality. Discontinuing such medications increases the risk of return to illicit opioid use, overdose, and death. The suggestion that patients should self-substitute a drug (ie, cannabis) that has not been subjected to a single clinical trial for opioid addiction is irresponsible and should be reconsidered.

These approaches reflect the stigmatized nature of people with opioid addiction that cannabis therapy might be considered reasonable with no clinical trials when no comparable provision has been made for other chronic diseases for which claims of cannabis' benefits have been made (eg, no regulations have suggested that patients with diabetes stop taking insulin and take cannabis instead). The recommendation is consistent with a history of medical professionals arguing that a different class of addictive drug will eliminate an addiction. For instance, in the past, morphine had been promoted as a cure for alcohol use disorder; cocaine as a cure for morphine addiction and alcohol use disorder; and heroin as a cure for alcohol use disorder, morphine addiction, and cocaine addiction.

## Risks of Cannabis Use

Unlike opioids, cannabis appears to have no risk of fatal overdose. However, systematic reviews find increased

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risks of motor vehicle crashes, cognitive impairment, structural brain changes, and psychotic symptoms.[1,7] The risk of cannabis addiction should be mentioned, particularly when the rationale for substitution is to prevent or treat addiction in people with or at risk for cannabis and other substance addiction. In a national population-based survey of 36 309 adults, the prevalence of cannabis use disorder was 31% among those reporting any use in the past year.[8] Cannabis addiction means use that causes clinically significant impairment or distress, including use that is out of control (the person tries to reduce use and cannot); craving; and recurrent social, occupational, and physical consequences. Cannabis use is also prospectively associated with a greater risk for other substance use disorders. All of these risks must be considered in light of the lack of evidence that taking cannabis while using opioids will necessarily result in a tapering of opioid dose, ie, it is entirely possible that these risks associated with cannabis will be added to those of opioid use.

## If Cannabis Is Recommended Medicine, It Should Be Held to Medical Standards

Clinical trials of opioids are of preparations of medications manufactured and regulated by national standards, which test specified doses, frequencies, and routes of administration. The known risks and benefits are derived from such studies. In clinical practice, clinicians prescribe the studied medications. These practices are not used for cannabis. Most clinical trials do not provide comparable evidence for medical cannabis. Medical cannabis regulations make unregulated products available to be inhaled in smoke or vapor, applied topically as oils and creams, eaten in edibles, or taken orally or sublingually. The demonstrated efficacy and safety of these products should not be labeled as medical, "Budtenders," not pharmacists, physicians, or other clinicians, make clinical recommendations. In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.[9] Ecological correlational studies and individual testimonials of benefit are not the quality of evidence typically required to recommend a medication for clinical use. Vulnerable and stigmatized patients with chronic pain and patients with addiction desperate for help are those exposed to such treatments, likely with no recourse if adverse effects occur (Food and Drug Administration–level assertions of safety and efficacy do not exist, and malpractice is likely not applicable).

## Conclusions

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,[3] 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.

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# Marijuana Use is Associated with Worse Outcomes in Symptom Severity and Violent Behavior in Patients with PTSD

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## Abstract

**Objective:** An increasing number of states have approved posttraumatic stress disorder (PTSD) as a qualifying condition for medical marijuana, though little evidence exists evaluating the effect of marijuana use in PTSD. We examined the association between marijuana use and PTSD symptom severity in a longitudinal, observational study.

**Methods:** From 1992-2011, veterans with PTSD (N=2276) were admitted to specialized VA treatment programs with assessments conducted at intake and four months after discharge. Subjects were classified into four groups according to marijuana use: those with no use at admission or after discharge (“never used”); those who used at admission but not after discharge (“stoppers”); those who used at admission and after discharge (“continuing users”); and those using after discharge but not at admission (“starters”). Analyses of variance compared baseline characteristics and identified relevant covariates. Analyses of covariance then compared groups on follow-up measures of PTSD symptoms, drug and alcohol use, violent behavior, and employment.

**Results:** After adjusting for relevant baseline covariates, marijuana use was significantly associated with worse outcomes in PTSD symptom severity, violent behavior, and measures of alcohol and drug use. At follow up, stoppers and never users had the lowest levels of PTSD symptoms ($p<0.0001$) and starters had the highest levels of violent behavior ($p<0.0001$). After adjusting for covariates and using never users as a reference, starting marijuana had an effect size on PTSD symptoms of +0.34 (Cohen’s $d$ = change/SD) and stopping marijuana had an effect size of −0.18.

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**Conflicts of Interest:** None

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**Declaration of Interest:** None.

**Additional Information:** The Intensive PTSD VA Treatment data base is managed by the VA New England Mental Illness Research and Education Center, West Haven, CT. They are on secure VA servers and are not available to the public. Queries can be directed to Robert Rosenheck, MD (robert.rosenheck@yale.edu).

**Conclusions:** In this observational study, initiating marijuana use after treatment was associated with worse PTSD symptoms, more violent behavior and alcohol use. Marijuana may actually worsen PTSD symptoms or nullify the benefits of specialized, intensive treatment. Cessation or prevention of use may be an important goal of treatment.

## INTRODUCTION:

Considerable interest and controversy has arisen regarding the clinical benefits and risks of marijuana for the treatment of various medical conditions.[1] Medical marijuana is now legal in at least 23 states,[2] although it remains illegal under federal law. Approval has come through state legislative processes or by direct popular vote and thus medical marijuana has not met scientific standards typically required by the Food and Drug Administration.[3] Posttraumatic stress disorder (PTSD) has been approved in at least nine states as a qualifying condition for medical marijuana.[2] However, thus far, little is known about the effect of marijuana on PTSD; there have been no randomized controlled trials evaluating its efficacy or safety.

Pre-clinical studies suggest that specific cannabinoids (cannabidiol) may show therapeutic promise in treating PTSD.[4, 5] Survey studies suggest that PTSD patients report feeling better subjectively as a result of marijuana use[6] and that patients who use marijuana are more likely to report doing so to help them cope with their symptoms.[7-9] Other studies suggest, to the contrary, that PTSD contributes to the development of cannabis use disorder.[10, 11] At best, the most rigorous studies merely show a non-causal association between PTSD and marijuana use.[12] The only longitudinal studies thus far involve a VA inpatient treatment program; these show that less improvement in PTSD during treatment was associated with greater risk of marijuana use at follow up[13] and that the presence of a marijuana use disorder at admission is associated with less improvement in PTSD symptoms.[14] These studies, however, did not exclude veterans with other forms of substance use or alcohol misuse and did not directly compare outcomes for veterans who initiated cannabis use with outcomes for veterans who stopped using or never used marijuana. All other studies to date have been cross-sectional in nature and thus have failed to address any longitudinal relationship between symptom severity in PTSD and subsequent marijuana use.

In 1992, the Veterans Health Administration system implemented a national data collection system that monitored outcomes of over 47,000 veterans treated in specialized intensive PTSD programs through 2011.[15] Here we present data from all sites participating in this national program evaluation effort over a 20-year period. None of the veterans were prescribed medical marijuana. However, as part of the program evaluation, data was collected on voluntary use of marijuana in the 30 days prior to program entry and again in the prior 30 days, 4 months after discharge. Because of the large sample size, we were able to identify subsamples who reported marijuana use but no other use of drugs or use of alcohol to intoxication at the time of admission as well as veterans who reported no drug use at all. We have thus been able to examine the relationship between change in marijuana use (in the absence of other initial drug or alcohol misuse) and change in PTSD symptoms and other outcomes (violent behavior, employment, and alcohol use), which we chose based on their important association with PTSD.[16-19] Based on previous literature showing that

substance use is associated with worse PTSD symptom outcomes,[20] we hypothesized that marijuana use would likewise be associated with greater symptom severity.

## METHODS:

The study was approved by the Institutional Review Board of the West Haven Center of the VA Connecticut Healthcare System and was given a waiver of informed consent.

### Participants

Data were drawn from the national evaluation of specialized intensive PTSD programs implemented by the Northeast Program Evaluation Center (NEPEC) of the Veterans Health Administration from 1992-2011. All patients entering these programs were evaluated at baseline and 4 months after discharge using a standardized set of sociodemographic and clinical measures. The sample from which the subjects were selected included 47,310 veterans with a diagnosis of PTSD (DSM-III criteria until 1994; DSM-IV criteria thereafter). To minimize confounding from the effects of substances other than marijuana, we excluded subjects with problematic alcohol use (more than two drinks on one occasion), with any drug use other than marijuana in the 30 days prior to admission, and those who entered treatment on transfer from an inpatient of residential program that would have restricted their access to alcohol or drugs. Any drug use was defined as having reported use of any other substances (cocaine, amphetamines, crack cocaine, heroin, “downers” or hallucinogens) besides cannabis. From the initial sample of 47,310 patients, 12,770 were found to meet inclusion criteria, according to the following groups: (1) those who reported no marijuana use prior to admission or after discharge (N=11,344) – “never used”; (2) those reporting marijuana use at admission but not at 4 months after discharge (N=299)– “stoppers”; (3) those reporting use at admission and 4 months after discharge (N=296) – “continuing users”; and (4) those who reported no use at admission but reported use 4 months after discharge (N=831)– “starters.” We considered the last group (starters) to be a rough proxy for those who might have used medical marijuana for PTSD. To provide more balanced samples, 850 subjects were randomly selected from the “never used” group, yielding a total analytic sample of 2,276 veterans.

### Measures

Measures available from the dataset included sociodemographic characteristics, clinical data (PTSD symptom severity, other comorbid psychiatric diagnoses, history of psychiatric hospitalization, drug and alcohol use severity measures, chronic medical problems), community adjustment variables, and treatment program characteristics. Outcomes included 4-month follow up assessments of PTSD symptom severity, employment status, violent behavior, and composite measures of alcohol and drug use from the Addiction Severity Index (ASI).[21]

**Clinical Data—**PTSD symptom severity was measured by the Short Form of the Mississippi Scale (MISS) for PTSD (range 11-55), which has been described and validated elsewhere.[22] Other measures addressed the participation in or witnessing of atrocities by

self-report, history of war-zone service, and receipt of service-connected disability benefits related to PTSD.

**Treatment Program Characteristics—**Characteristics of treatment program included discharge status, length of stay (LOS), year of admission to program, and whether the veteran had been on a waiting list prior to admission to the program. Discharge status reflected the conditions under which the veteran left the program and were classified as: having successfully completed the program; departure associated with unacceptable behavior or violation of program rules; choosing to leave prematurely (without staff concurrence); being assessed as too sick to continue in the program; or being transferred to another program.

**Community Adjustment Variables—**Variables assessing a veteran's community adjustment included employment status, violent behavior, history of incarceration, and whether the veteran was planning on attending military reunions after discharge. Employment status was assessed as the average number of days a veteran had worked for pay in the previous 30 days using items from the ASI [21]. Violent behavior was assessed using a four-item self-report questionnaire from the National Vietnam Veterans Readjustment Study.[23]

## Data Analysis

First, analysis of variance (ANOVA) was used to compare baseline characteristics of the four marijuana use groups (never users, starters, stoppers, or continuing users). These characteristics (sociodemographic features, baseline clinical variables, community adjustment variables, and characteristics of program participation) could potentially confound comparison of post-discharge outcomes between the groups. Because five outcome measures were examined and the sample size was substantial, an alpha level of 0.01 was used to test for statistical significance.

Variables that were found to be significant on the bivariate analysis were used as covariates in a subsequent analysis of covariance (ANCOVA) which compared the groups at follow-up on PTSD symptoms and other outcomes net of potential baseline confounders. If the overall ANCOVA was significant at $p<0.01$, t-tests were used to compare adjusted means. Subsequently, a linear multiple regression analysis including all marijuana users (whether at baseline or follow-up) was conducted to examine the association of change in days of marijuana use from before to after program entry and change in PTSD symptoms, violent behavior, days of employment, and the ASI alcohol and drug use composite scores, again controlling for potential baseline confounders, including the baseline values of the change variables (to adjust for regression to the mean). Standardized regression coefficients were used to evaluate the strength of association between change in days of marijuana use and change in other outcomes.

# RESULTS

## General sample characteristics

The sample consisted of 2,276 veterans with an average age of 51.7 years (SD=8.6); the majority (96.7%) were male. Most were white (72.7%), while 21.2% were African American and 6.1% were reported as 'other'. Married veterans comprised 40.7% of the sample, while an equivalent portion (40.7%) were separated/divorced and 1.9% were widowed. The average education level of the sample was 12.9 years (SD=1.9). A slight majority (51.4%) had a history of incarceration. Comorbid psychiatric diagnoses included affective disorder (28.4%), anxiety disorder (12.2%), personality disorder (8.2%), bipolar disorder (4.3%), psychosis other than schizophrenia (1.9%), and schizophrenia (0.8%). Most (86.2%) had been prescribed psychotropic medications in the past 30 days and most (63.6%) entered the treatment program from waiting list status. The average length of stay was 42.5 days (SD=22.8).

## Bivariate Analysis

Participants who never used marijuana were slightly older (53.2 years) than other groups and more likely to be married than continuing users and starters (46.5% v. 37.2% and 36.3%, respectively) (Table 1). They also had the lowest baseline ASI composite scores for both alcohol and (unsurprisingly) drugs. Generally, this group (never users) had better measures of community adjustment, with lower rates of incarceration (compared to starters and continuing users), lower measures of violent behavior (compared to stoppers and starters), and they were more likely to plan to attend reunions after discharge (compared to stoppers and continuing users). Veterans who were using marijuana at admission (continuing users and stoppers) had higher measures of violent behavior prior to admission than those who never used before or after the program. In measures of treatment process, continuing users had shorter lengths of stay compared to never users and starters (38.2 v. 44.8 and 42.8 days, respectively) and were less likely to be on a waiting list than never users and starters (53.9% v. 68.2% and 64.9%, respectively). Other than history of war-zone service, groups did not differ in measures of PTSD or other psychiatric disorders. Other variables that had a statistically significant association with marijuana use groups ($p<0.01$) included race, chronic medical problems, employment status at admission, and number expelled from the program. All variables that had significant ($p<0.01$) interaction with marijuana use groups were included as covariates in subsequent examination of clinical variables at follow up.

## Clinical and Community Adjustment Outcomes

After adjusting for relevant covariates, ANCOVAs revealed significant differences among marijuana use groups in several outcome measures (Table 2), including PTSD symptom severity. Starters and continuing users had significantly higher measures of PTSD symptom severity at follow up compared to never users and stoppers. Starters showed significantly higher measures of violent behavior at follow up than all other groups. In measures of alcohol problems at follow up, starters had the highest measures while stoppers had lower measures than continuing users but did not differ from never users. Stoppers and never users had lower composite scores of drug abuse (ASI) than continuing users and starters at follow up. After adjusting for covariates and using never users as a comparison, starting marijuana

had an effect size on PTSD symptoms at follow-up of +0.34 (Cohen's *d* = change/SD) and stopping marijuana had an effect size of −0.18. There was no difference at follow up among the groups in employment status. Additional multivariate regression analyses, controlling for covariates identified previously, yielded similar results, with significant associations as measured by standardized regression coefficients between change in days of marijuana used and: change in PTSD symptoms (β=0.17, t=4.08, p<0.0001); severity of violent behavior (β=0.10, t=2.79, p=0.0054); the ASI alcohol index (β=0.24, t=5.60, p<0.0001); and the ASI drug abuse index (β=0.65, t=21.62, p<0.0001).

## DISCUSSION

This is the first longitudinal study of the association of marijuana use with PTSD symptom severity and other outcomes that excluded the potentially confounding effect of baseline use of other drugs or problematic alcohol use. These data show that initiating marijuana was associated with higher measures of PTSD symptoms at follow up, with a modest effect size (*d*=0.34) compared to never users. Stopping marijuana use during treatment, in contrast, was associated with the greatest improvement in PTSD. Regression analyses showed statistically significant positive associations between increased days of marijuana use and: more severe PTSD symptoms, violent behavior, and alcohol use, but not with days of employment. This study cannot exclude the possibility that PTSD patients refractory to treatment are more likely to use marijuana in an attempt to self-medicate.

Our findings are consistent with previous longitudinal studies of the relationship between marijuana use and PTSD[13, 14] and with a previous study of substance use more generally in PTSD.[20] However, this study extends previous literature by directly comparing outcomes among those who begin marijuana use following treatment, those who stop use during treatment, those who continued to use before and after treatment, and those who never used. Further, our larger sample size and refined exclusion criteria (i.e., recent use of other drugs and intoxication with alcohol) provide a purer sample more capable of isolating the association of initiating marijuana use among veterans with PTSD and subsequent symptom severity. Although our use of the starter group as a rough proxy for medical marijuana use is imperfect and does not take into account the frequency or quantity (i.e., dosing) of recommended use for medical marijuana, it should be noted that the concept of a prescribed dose in the medical marijuana literature has not been specified and most clinical trials of medical marijuana allow patients to self-titrate based on symptoms and tolerability.

These findings can be contextualized within existing literature suggesting that patients feel marijuana use is helpful in the treatment of PTSD.[6, 24] The data are associational and allow for the possibility that patients with PTSD refractory to specialized, intensive treatment begin marijuana use in an effort to self-medicate. This is highlighted by the fact that among all 'pure' marijuana users in this study (N=1426), over half (N=831, 58%) began use after treatment. Previous research also suggests that patients feel other substances (alcohol, heroin, benzodiazepines) may alleviate PTSD symptoms,[6] but more objective assessments indicate that these substances are generally associated with worse outcomes.[20, 25] Our findings do not suggest, however, that marijuana is associated with improvement in PTSD. Previous evidence suggesting that marijuana improves PTSD symptoms come from isolated

case reports[24] or studies methodologically weakened by recall bias and/or post-hoc subjective assessment of symptom severity.[6, 26] Such biases are minimized in the current longitudinal study based on standard psychometric data. Another possible interpretation of these data is that marijuana use in patients with PTSD provides transient relief but that subsequent periods of withdrawal contribute to a worsening of baseline symptoms. Hence, while patients may feel that marijuana improves their PTSD, it may contribute to an overall worsening of the disorder. This is consistent with previous literature characterizing marijuana use in PTSD as a "pernicious feedback loop"[8] and is consistent with existing theories explaining the high comorbidity of PTSD and substance abuse generally.[27]

An unanticipated finding was the robust association of the initiation of marijuana use with higher follow up measures of violent behavior. Previous literature regarding the association between cannabis use and violence is inconsistent.[28-31] Despite its popular reputation as a drug that does not induce violence, cannabis has been shown in some populations (adolescents, inner city youth) to be associated with violent behavior.[32, 33] The only study to date examining an association between marijuana use and violence in a population diagnosed with PTSD found that patients with a recent history of violence were more likely to report recent marijuana use.[34] Our finding that those who started using marijuana in the months after completing treatment had higher overall rates of violent behavior could be partially explained by the fact that starters also had higher rates of alcohol use at follow up (which is associated with violence[35, 36]) and that marijuana withdrawal symptoms include irritability and aggression.[37] Another possible interpretation is that the association between marijuana use and violence represents a selection effect or "general deviance syndrome",[32] where individuals who are more impulsive or prone to breaking rules/laws resort to violence as well as marijuana in the face of stress or problem situations; however, these interpretations cannot explain why starters had higher rates of violence at follow up compared to continuing users.

Strengths of the current study include exclusion of subjects who recently used drugs other than marijuana or experienced alcohol intoxication, a large sample size, adjustment for multiple potentially confounding factors, and the longitudinal nature of the study, albeit with a relatively short follow-up period. Despite the robust statistical findings of this study, several limitations require comment. First, patients were not randomized to receive marijuana or placebo and thus the groups cannot be considered to have been equivalent at the time of program entry. Hence these data are associational in nature and cannot be taken as demonstrating causal relationships. Unmeasured differences between the groups at the time of program entry in areas such as impulsivity or antisocial behavior may explain both worsening symptoms and marijuana use. Second, drug use was assessed by self-report and not verified by toxicological testing. Third, we could not assess or control for the varying levels of cannabinoids in the marijuana used. This point is significant because delta-9-tetrahydrocannabinol, which is responsible for the euphoria associated with the drug, has been shown to exacerbate anxiety,[38] while cannabidiol has anxiolytic properties.[39-41] Fourth, our sample was limited to older, mostly male veterans suffering from longstanding PTSD. The generalizability of our study to other populations is unknown. Finally, our assessments were conducted when veterans were presumably not under the immediate

influence of marijuana. It does not address the possibility that some veterans do receive transient symptomatic relief while intoxicated.

The above limitations notwithstanding, our study has suggestive implications for clinical practice and public policy. The results of our study provide no support for the hypothesis that marijuana is associated with general improvement in PTSD symptoms and the observed associations suggest that it may actually worsen PTSD symptoms or nullify the benefits of specialized, intensive treatment. Especially in light of the adverse health effects of marijuana use,[1] these data indicate that providers should be cautious or even avoidant in using this agent to treat PTSD. Given that our study only shows associations and not causation, it remains possible that more severe PTSD symptoms drive people to seek marijuana to transiently self-medicate symptoms. Prospective randomized clinical trials would be needed to establish a more definitive understanding of the impact of marijuana use on individuals with PTSD.

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**Clinical Points:**

- Medical marijuana has been approved for treatment of post-traumatic stress disorder (PTSD) in several states, despite an absence of clinical trials evaluating efficacy and safety
- Psychiatrists are frequently asked whether they would recommend marijuana for PTSD
- This study shows that starting marijuana use may be associated with worse outcomes in PTSD

**Table 1.**

Demographic, Clinical, Community and Treatment Characteristics[a]

| | Never Users (1) N=850 | Sbottompers (2) N=299 | Continuing Users (3) N=296 | Starters (4) N=831 | F value | P value | Paired comparisons* |
|---|---|---|---|---|---|---|---|
| | Mean *(SD)* / N(%) | | | | | | |
| **Demographic Variables** | | | | | | | |
| Male | 568 *(96.1)* | 210 *(95.5)* | 223 *(97.0)* | 573 *(97.8)* | 1.32 | 0.2669 | |
| Age (years) | 53.15 *(8.13)* | 49.28 *(9.64)* | 49.77 *(10.02)* | 51.76 *(7.97)* | 21 | <0.0001 | 1>4>2,3 |
| Highest Level School (Years) | 12.83 *(2.05)* | 12.94 *(1.87)* | 13.09 (1.73) | 12.86 *(1.89)* | 1.54 | 0.2024 | |
| *Marital Status:* | | | | | | | |
| Married | 395 *(46.5)* | 119 *(39.8)* | 110 *(37.2)* | 302 (36.3) | 6.68 | 0.0002 | 1>3,4 |
| Separated/divorced | 308 *(36.2)* | 117 *(39.1)* | 129 (43.6) | 373 *(44.9)* | 4.81 | 0.0024 | 4>1 |
| Widowed | 16 *(1.9)* | 10 *(3.3)* | 6 *(2.0)* | 13 *(1.6)* | 1.22 | 0.3012 | |
| *Race* | | | | | | | |
| White | 597 *(70.2)* | 215 *(72.4)* | 243 *(82.1)* | 597 *(71.9)* | 5.37 | 0.0011 | 3>1,2,4 |
| African American | 212 *(24.9)* | 61 *(20.5)* | 36 *(12.2)* | 173 *(20.8)* | 7.30 | <0.0001 | 1,4>3 |
| Other | 41 *(4.8)* | 21 *(7.1)* | 16 *(5.4)* | 60 *(7.2)* | 1.67 | 0.1704 | |
| **Clinical Variables** | | | | | | | |
| *Baseline PTSD Measures* | | | | | | | |
| Symptom Severity (MISS), Baseline | 39.63 *(6.00)* | 39.87 *(5.40)* | 39.73 *(5.59)* | 40.20 *(5.72)* | 1.42 | 0.2347 | |
| Witnessed Atrocities | 202 *(23.8)* | 69 *(23.1)* | 72 *(24.3)* | 213 *(25.7)* | 0.39 | 0.7613 | |
| Participated in Atrocities | 138 *(16.2)* | 45 *(15.1)* | 51 *(17.2)* | 165 *(19.9)* | 1.80 | 0.1458 | |
| Service-connected PTSD | 468 *(55.3)* | 155 *(52.2)* | 161 *(54.4)* | 452 *(54.4)* | 0.29 | 0.8326 | |
| War Zone Service (P17) | 795 *(93.6)* | 275 *(92.3)* | 259 *(87.5)* | 783 *(94.2)* | 5.40 | 0.0011 | 1,4>3 |
| *Other Psychiatric Disease* | | | | | | | |
| Anxiety Disorder | 119 *(14.0)* | 29 *(9.7)* | 43 *(14.5)* | 86 *(10.4)* | 2.82 | 0.0378 | |
| Affective Disorder | 254 *(29.9)* | 87 *(29.2)* | 86 *(29.3)* | 219 *(26.4)* | 0.92 | 0.4290 | |
| Bipolar Disorder | 32 *(3.8)* | 19 *(6.4)* | 12 *(4.1)* | 34 *(4.1)* | 1.29 | 0.2777 | |
| Schizophrenia | 8 *(0.9)* | 2 *(0.7)* | 3 *(1.0)* | 7 *(0.8)* | 0.09 | 0.9678 | |
| Psychosis, Other than Schizophrenia | 19 *(2.2)* | 7 *(2.4)* | 4 *(1.4)* | 14 *(1.7)* | 0.49 | 0.6912 | |
| Personality Disorder | 62 *(7.3)* | 23 *(7.7)* | 28 *(9.5)* | 74 *(8.9)* | 0.74 | 0.5269 | |

| | Never Users (1) N=850 | Sbottompers (2) N=299 | Continuing Users (3) N=296 | Starters (4) N=831 | F value | P value | Paired comparisons* |
|---|---|---|---|---|---|---|---|
| | Mean *(SD)* / N(%) | | | | | | |
| Other Psychiatric Disorder | 34 *(4.0)* | 14 *(4.7)* | 14 *(4.8)* | 38 *(4.6)* | 0.17 | 0.9190 | |
| Ever Hospitalized (psychiatric) | 677 *(79.7)* | 278 *(93.0)* | 265 *(89.5)* | 735 *(88.6)* | 2.22 | 0.0838 | |
| Prescribed Psychotropic Medication, Last 30 Days | 738 *(86.8)* | 247 *(82.6)* | 258 *(87.2)* | 720 *(86.6)* | 1.30 | 0.2735 | |
| *Drug, Alcohol Use* | | | | | | | |
| Drug Abuse at Admission (ASI) | .0259 *(.039)* | .1027 *(.100)* | .1139 *(.097)* | .0394 *(.061)* | 195.17 | <0.0001 | 2,3>4>1 |
| Alcohol Abuse at Admission (ASI) | .0634 *(.098)* | .0984 *(.116)* | .0863 *(.086)* | .0804 *(.119)* | 9.62 | <0.0001 | 2,3,4>1 |
| *Other Medical Problems* | | | | | | | |
| Number with Chronic Medical Problems | 631 *(74.4)* | 192 *(64.2)* | 203 *(68.6)* | 578 *(69.6)* | 4.28 | 0.0050 | 1>2 |
| **Community Adjustment Variables** | | | | | | | |
| Employment Status at Admission (ASI) | .589 *(.258)* | .536 *(.273)* | .592 *(.242)* | .560 *(.259)* | 4.33 | 0.0048 | 1,3>2 |
| Days Worked in the Past 30 | 3.39 *(8.13)* | 2.43 *(6.57)* | 3.14 *(7.52)* | 2.58 *(7.01)* | 1.96 | 0.1174 | |
| Violence at Admission | 1.37 *(1.36)* | 1.63 *(1.32)* | 1.48 *(1.28)* | 1.68 *(1.42)* | 7.57 | <0.0001 | 2,4>1 |
| Number with History of Incarceration | 366 *(43.2)* | 153 *(51.2)* | 165 *(55.7)* | 485 *(58.4)* | 14.14 | <0.0001 | 3,4>1 |
| Number Willing to Attend Reunions | 599 *(70.9)* | 168 *(56.8)* | 151 *(51.7)* | 534 *(65.4)* | 15.05 | <0.0001 | 1,4>2,3 |
| **Treatment Characteristics** | | | | | | | |
| Length of Stay in Program | 44.8 *(22.4)* | 39.3 *(23.9)* | 38.2 *(25.2)* | 42.8 *(22.0)* | 8.10 | <0.0001 | 1>2,3; 4>3 |
| Year of Program Admission | 2002.7 *(4.5)* | 2003.0 *(5.0)* | 2003.5 *(5.1)* | 2002.6 *(4.7)* | 2.68 | 0.0454 | |
| Expelled from Program | 16 *(1.9)* | 24 *(8.1)* | 9 *(3.1)* | 24 *(2.9)* | 9.18 | <0.0001 | 2>1,3,4 |
| Transferred from Program | 10 *(1.2)* | 7 *(2.4)* | 2 *(0.7)* | 9 *(1.1)* | 1.30 | 0.2730 | |
| Left Program Without Staff Concurrence | 30 *(3.6)* | 13 *(4.4)* | 21 *(7.2)* | 25 *(3.1)* | 3.39 | 0.0173 | |
| Too Sick for Program | 4 *(0.5)* | 0 *(0)* | 2 *(0.7)* | 3 *(0.4)* | 0.64 | 0.5900 | |
| Was on Waiting List | 578 *(68.2)* | 166 *(56.3)* | 158 *(53.9)* | 535 *(64.9)* | 9.07 | <0.0001 | 1,4>2,3 |

[a]Data are incomplete for gender (28.5%), days worked in the past 30 (10%), and <1.2% of the following variables: age, education, race, PTSD symptom severity, witnessing atrocities, PTSD service-connection, other psychiatric diseases, drug and alcohol abuse at admission, chronic medical problems, and community adjustment and treatment characteristic variables

*P < 0.01

Abbreviations: SD - Standard Deviation; ASI - Addiction Severity Index; MISS - Mississippi Short Form scale

**Table 2.**

Relationship Between Marijuana Use and Clinical Outcomes at 4 Months Follow Up

| Outcome Variable | Never Users (1) N=767 | Stoppers (2) N=263 | Continuing Users (3) N=268 | Starters (4) N=738 | F value | P value | Paired comparisons* |
|---|---|---|---|---|---|---|---|
| | LS Mean[a] *(SE)* | | | | | | |
| PTSD Symptom severity (MISS) | 37.71 *(0.228)* | 36.64 *(0.385)* | 38.92 *(0.383)* | 39.67 *(0.226)* | 21.47 | <0.0001 | 3,4>1,2 |
| Violence | 0.87 *(0.041)* | 0.76 *(0.068)* | 0.93 *(0.068)* | 1.25 *(0.040)* | 21.28 | <0.0001 | 4>1,2,3 |
| Alcohol Abuse (ASI) | 0.096 *(0.007)* | 0.079 *(0.011)* | 0.129 *(0.011)* | 0.229 *(0.006)* | 88.51 | <0.0001 | 4>1,2,3; 3>2 |
| Drug Abuse (ASI) | 0.037 *(0.0033)* | 0.034 *(0.0056)* | 0.128 *(0.0056)* | 0.13 *(0.0033)* | 176.26 | <0.0001 | 3,4>1,2 |
| Employment Status (ASI) | 0.578 *(0.007)* | 0.575 *(0.011)* | 0.594 *(0.011)* | 0.577 *(0.007)* | 0.66 | 0.5752 | |

[a]Covarying for marital status; age; race; history of incarceration; waiting list status; psychosis; chronic medical problems; war zone service; length of stay; expulsion from treatment; and baseline measures of violence, PTSD, drug and alcohol abuse, and employment

*P < 0.01

Abbreviations: LS - Least Squares; SE - Standard error; MISS - Short Form of the Mississippi; ASI - Addiction Severity Index

# Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study

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## Summary

**Background** The risk of individuals having adverse effects from drug use (eg, alcohol) generally depends on the frequency of use and potency of the drug used. We aimed to investigate how frequent use of skunk-like (high-potency) cannabis in south London affected the association between cannabis and psychotic disorders.

**Methods** We applied adjusted logistic regression models to data from patients aged 18–65 years presenting to South London and Maudsley NHS Foundation Trust with first-episode psychosis and population controls recruited from the same area of south London (UK) to estimate the effect of the frequency of use, and type of cannabis used on the risk of psychotic disorders. We then calculated the proportion of new cases of psychosis attributable to different types of cannabis use in south London.

**Findings** Between May 1, 2005, and May 31, 2011, we obtained data from 410 patients with first-episode psychosis and 370 population controls. The risk of individuals having a psychotic disorder showed a roughly three-times increase in users of skunk-like cannabis compared with those who never used cannabis (adjusted odds ratio [OR] 2·92, 95% CI 1·52–3·45, p=0·001). Use of skunk-like cannabis every day conferred the highest risk of psychotic disorders compared with no use of cannabis (adjusted OR 5·4, 95% CI 2·81–11·31, p=0·002). The population attributable fraction of first-episode psychosis for skunk use for our geographical area was 24% (95% CI 17–31), possibly because of the high prevalence of use of high-potency cannabis (218 [53%] of 410 patients) in our study.

**Interpretation** The ready availability of high potency cannabis in south London might have resulted in a greater proportion of first onset psychosis cases being attributed to cannabis use than in previous studies.

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## Introduction

Cannabis is the most popular illicit drug in the world. Uruguay was the first country to legalise its use and several US states have done so or are in the process of doing similar.[1] Therefore, any harm caused by cannabis use should be quantified. Prospective epidemiological studies have consistently reported that use of cannabis increases the risk of schizophrenia-like psychosis.[2,3] In the UK, the investigators of the 2012 Schizophrenia Commission[4] concluded that cannabis use is the most preventable risk factor for psychosis, and research that aims to improve estimation of the drug's contribution to illness development should be pursued.

The aspects of exposure to cannabis (eg, age at first use, frequency of use, duration of use) that confer the greatest effect on risk of psychosis are unclear. Such information would be valuable for public education and to estimate the proportion of psychosis cases that could be prevented if harmful patterns of cannabis use were removed from the population. The few studies[5,6] that have tried to estimate the effect of cannabis use on the number of new cases of psychosis in specific populations have been limited by the scarcity of accurate information on patterns of cannabis use.

The risk of adverse effects for mental health and cognition posed by cannabis use has been suggested to depend on the potency of the type of cannabis used.[7] For example, in a previous study[8] of part of the population reported here, we noted that skunk-like types of cannabis, which contain very high concentrations of Δ-9-tetrahydrocannabinol (THC), seemed to have a greater psychotogenic effect than did hash (resin), which is known to contain much less THC.

We analysed detailed data for history of cannabis use, aiming to: compare the patterns and types of cannabis used between patients with first-episode psychosis and a

population control sample; use the data for pattern of cannabis use to develop a cannabis exposure measure that accurately estimates the risk of psychotic disorders; and calculate the proportion of cases of psychosis in our study area attributable to use of cannabis, particularly high-potency cannabis, if we assumed causality.

## Methods

### Study design and participants

As part of the GAP study,[8] we did a case-control study at the inpatient units of the South London and Maudsley (SLaM) NHS Foundation Trust. We approached all patients aged 18–65 years who presented with first-episode psychosis. We invited patients to participate if they met the International Classification of Diseases 10 criteria for a diagnosis of non-affective (F20–F29) or affective (F30–F33) psychosis, validated by administration of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[9] We excluded individuals who met the criteria for organic psychosis (F09). If patients were too unwell to cooperate, we re-contacted them after the start of treatment.

We recruited controls using internet and newspaper advertisements and by distributing leaflets at train stations, shops, and job centres. None of the advertising material mentioned cannabis or illicit drug use. Volunteers were administered the Psychosis Screening Questionnaire[10] and were excluded if they met the criteria for a psychotic disorder or if they reported a previous diagnosis of psychotic illness. This study is part of the GAP study, which was granted ethical approval by SLaM and Institute of Psychiatry Local Research Ethics Committee. All case and control individuals included in the study gave written informed consent.

### Procedures

We obtained sociodemographic data using the Medical Research Council Schedule.[11] From March, 2006, we took a more detailed history of cannabis use by adding the Cannabis Experience Questionnaire modified version ($CEQ_{mv}$) to the assessment.[8,12] From the $CEQ_{mv}$, we derived information on history of use of tobacco, alcohol, other recreational drugs, and detailed information on cannabis use (age at first use, duration of use, frequency of use, type used).

Measures of cannabis use relevant to the analysis were: lifetime history of cannabis use—ie, had the individual ever used cannabis at any point in their life (no scores 0, yes scores 1); lifetime frequency of cannabis use—ie, the frequency that characterised the individual's most consistent pattern of use (none scores 0, less than once per week every week scores 1, at weekends scores 2, every day scores 3); and type of cannabis used—ie, the type most used by the subject (none scores 0, low potency [hash-type] scores 1, high potency [skunk-type] scores 2). This variable was grouped in accordance with the characteristics of the cannabis samples seized by the Metropolitan Police in London, as reported by Potter and colleagues[13] and the Home Office study (appendix).[14] Finally, we used a seven-item composite cannabis exposure measure derived from the lifetime frequency of use and the most used type (none scores 0, hash less than once per week every week scores 1, hash at weekends scores 2, hash every day scores 3, skunk less than once per week scores 4, skunk at weekends scores 5, skunk every day scores 6) to investigate which patterns of use conferred the greatest risk.

See Online for appendix

### Statistical analysis

We analysed data using Stata 13. We used $\chi^2$ tests and *t* tests (or Mann-Whitney U tests) to test for associations between potential confounding variables and between presence of psychotic disorder and exposure to cannabis use. We also used these tests to establish whether missing data for the cannabis use exposure were associated with case-control status and therefore likely to bias the results.

We used logistic regression to analyse whether individual indicators of cannabis use (lifetime use, age at first use, duration and frequency of use, and most used type of cannabis) improved estimation of the likelihood of psychotic disorders (ie, case status), in comparisons of cannabis users with non-users.

We used the *punafcc* command in Stata 13 to estimate the population attributable fraction (PAF), with confidence intervals, for each cannabis use variable. The PAF measures the population effect of an exposure by providing an estimate of the proportion of disorder that would be prevented if the exposure were removed. However, causality does not have to be proven before the PAF can be estimated, and this causation is not usually established when PAFs are estimated (indeed no single study could ever prove causation). Because the same proportion of disorder attributable to a specific risk factor can also be attributable to other factors with which the specific risk factor might interact, PAFs for multiple risk factors can add up to more than 100%. Furthermore, the PAF depends on both the prevalence of exposure (ie, measures of cannabis use) in cases and the odds ratio (OR) for the exposure, such that a risk factor with a modest OR can have a major population effect if the factor is common.

### Role of the funding source

All funders contributed to data collection by providing the salaries of the research workers collecting the data. The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between May 1, 2005, and May 31, 2011, we approached 606 patients with first-episode psychosis. Of these 606 patients, 145 (24%) refused to participate. Thus, we recruited 461 patients with first-episode psychosis. Patients who refused to participate were more likely to be men ($p<0·004$) and of Black Caribbean and Black African ethnic

| | First-episode psychosis group (n=410) | Control group (n=370) | p value |
|---|---|---|---|
| Age, years | 27·1 (8·7) | 30·0 (9·0) | 0·0001 |
| Gender | .. | .. | 0·004 |
| Male | 271 (66%) | 209 (56%) | .. |
| Female | 139 (34%) | 161 (44%) | .. |
| Ethnic origin | .. | .. | 0·0001 |
| White | 132 (32%) | 212 (57%) | .. |
| Black Caribbean | 136 (33%) | 73 (20%) | .. |
| Black African | 98 (24%) | 38 (10%) | .. |
| Asian/other | 44 (11%) | 47 (13%) | .. |
| Education | .. | .. | 0·0003 |
| No qualification | 60 (15%) | 8 (2%) | .. |
| GCSEs | 116 (28%) | 31 (8%) | .. |
| A levels or vocational training | 153 (37%) | 151 (41%) | .. |
| University | 81 (20%) | 180 (49%) | .. |
| Ever employed | .. | .. | 0·001 |
| Yes | 361 (88%) | 353 (95%) | .. |
| No | 46 (11%) | 15 (4%) | .. |
| No details | 3 (1%) | 2 (1%) | .. |

Data are mean (SD) or n (%) unless stated otherwise.

***Table 1:*** **Population sociodemographics**

| | First-episode psychosis group (n=410) | Control group (n=370) | p value |
|---|---|---|---|
| **Total population** | | | |
| Lifetime history of cannabis use | .. | .. | 0·277 |
| Yes | 275 (67%) | 232 (63%) | .. |
| No (never used) | 135 (33%) | 138 (37%) | .. |
| Frequency of use | .. | .. | <0·0001 |
| Less than once per week | 68 (17%) | 128 (35%) | .. |
| At weekends | 84 (20%) | 63 (17%) | .. |
| Every day | 123 (30%) | 41 (11%) | .. |
| Most used type of cannabis | .. | .. | <0·0001 |
| Never used | 135 (33%) | 138 (37%) | .. |
| Hash-like | 57 (14%) | 162 (44%) | .. |
| Skunk-like | 218 (53%) | 70 (19%) | .. |
| **Cannabis users** | | | |
| Duration of use (years) | 9·7 (7·4) | 9·1 (7·8) | 0·635 |
| No details | 3 | 1 | .. |
| Age at first cannabis use (years) | 16·1 (4·2) | 16·6 (3·2) | 0·146 |
| No details | 3 | 1 | .. |
| Age at first use ≤15 years | .. | .. | 0·028 |
| No | 172 (63%) | 178 (77%) | .. |
| Yes | 100 (36%) | 53 (23%) | .. |
| No details | 3 | 1 | .. |

Data are n (%) or mean (SD) unless stated otherwise.

***Table 2:*** **Cannabis use**

origin (p=0·001) than were those who consented. Therefore, in all the analyses, we tested for the potential confounding effects of ethnic origin and gender. During the same period and from the geographical area served by the clinical units, we recruited 389 control individuals, aged 18–65 years, who were similar to the local population in terms of ethnic origin, education, and employment status (table 1). The later addition of $CEQ_{mv}$ meant that there were data missing on detailed patterns of cannabis use for those participants recruited early in the project. The data we present here are therefore based on 410 (89%) of 461 patients with first-episode psychosis and 370 (95%) of 389 controls for whom we had data for cannabis use.

The patients with first-episode psychosis consisted of more men and were younger than the control group (table 1). As noted previously,[15] patients with first-episode psychosis were also more likely to be of Black ethnic origin (Caribbean or African) compared with controls, and less likely to have completed a high level of education than were controls (table 1).

A larger proportion of patients with first-episode psychosis (184 [45%] of 410 individuals) reported having smoked 100 tobacco cigarettes or more than did controls (60 [16%] of 370 individuals; p<0·0001), but the groups did not differ in lifetime history of other substance use (p=0·615), or alcohol units consumed per week (p=0·083). Patients with first-episode psychosis were no more likely than were controls to report a lifetime history of ever having used cannabis, but were more likely to use cannabis every day and to mostly use high-potency (skunk-like) cannabis (table 2). A small proportion of cannabis users (3 [0·6%] of 507 individuals) reported having used cannabis more than four days a week and they were included in the every day category.

For more on **demographic composition of the local population** see www.statistics.gov.uk/census

Among cannabis users, the mean duration of use did not differ between patients with first-episode psychosis and controls (table 2). On average, both groups started using cannabis in their mid-teens, although distribution of the age at first cannabis use seemed to be skewed (mean 16·1 years, SD 4·2, median 16 years in the patients with first-episode psychosis *vs* mean 16·6 years, SD 3·2, median 17 years in the control group; Z=2·88; p=0·146). Patients with first-episode psychosis were more likely to start using cannabis at age 15 years or younger than were controls.

When we combined data on frequency of cannabis use and most used type into a single variable, the composite cannabis exposure measure, controls were more likely to be occasional users of low-potency cannabis (hash), and patients with first-episode psychosis were more likely to be daily users of high-potency cannabis (skunk; figure 1; p<0·0001).

A logistic regression, adjusted for age, gender, ethnic origin, number of cigarettes smoked, alcohol units and lifetime use of other illicit drugs, education, and employment history, showed that individuals who had ever used cannabis were not at increased risk of psychotic disorder compared with those who had never used

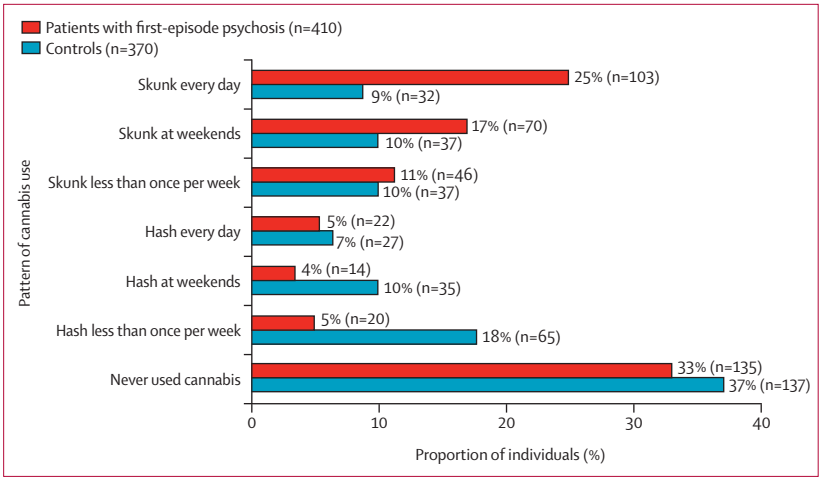


*Figure 1:* **Patterns of cannabis use between patients with first-episode psychosis and population controls**

| | Odds ratio* (95% CI) | p value |
|---|---|---|
| **Age at first use, years** | | |
| Never used | 1 | .. |
| ≥15 years | 0·68 (0·34–1·37) | 0·292 |
| <15 years | 1·55 (1·00–1·39) | 0·048 |
| **Frequency of use** | | |
| Never used | 1 | .. |
| Less than once per week | 0·58 (0·25–1·32) | 0·198 |
| Weekends | 1·04 (0·41–1·62) | 0·929 |
| Every day | 3·04 (1·91–7·76) | 0·020 |
| **Most used type** | | |
| Never used | 1 | .. |
| Hash-like | 0·83 (0·52–1·77) | 0·903 |
| Skunk-like | 2·91 (1·52–3·60) | 0·001 |

*Adjusted for age, gender, ethnic origin, number of cigarettes, alcohol units, other drugs used, education, and employment status.

*Table 3:* **Risk for first-episode psychosis for each measure of cannabis exposure**

cannabis (n=775 [data for employment history was missing for five participants, OR 0·93, 95% CI 0·67–1·52, p=0·569). Individuals who started using cannabis at ages younger than 15 years had modestly, but significantly, increased risk of psychotic disorders compared with those who never used cannabis (table 3). People who used cannabis or skunk every day were both roughly three times more likely to have a diagnosis of a psychotic disorder than were those who never used cannabis (table 3).

We used logistic regression (n=775) to test whether the composite cannabis exposure measure predicted risk of psychotic disorder more accurately than the individual markers, frequency of cannabis use and most used type of cannabis, alone. Individuals who mostly used low-potency (hash-like) cannabis occasionally (p=0·493), at weekends (p=0·102), or daily (p=0·626) had no increased likelihood of psychotic disorders compared with those who never used cannabis (figure 2).

Compared with those who never used cannabis, individuals who mostly used skunk-like cannabis were nearly twice as likely to be diagnosed with a psychotic disorder if they used it less than once per week (p=0·020), almost three times as likely if they used it at weekends (p=0·008), and more than five times as likely if they were daily users (p=0·001; figure 2).

Based on the estimated adjusted OR for daily cannabis use (3·04, 95% CI 1·91–7·76), we calculated that, if we assumed causality, 19·3% (13·1–27·0) of psychotic disorders in the study population were attributable to exposure to daily cannabis use. The PAF of psychotic disorders in the study population that were attributable to high potency cannabis use was 24·0% (17·4–30·6) and the PAF for the two exposures combined, skunk use every day, was 16·0% (14·0–20·3; table 4). If causality is assumed, this finding suggests that skunk alone was responsible for the largest proportion of new cases (24%) of psychotic disorder in the study population, an effect driven by its high prevalence among patients with first-episode psychosis who used cannabis (218 [53%] of 410 patients).

## Discussion

The results of our study support our previous conclusions from analysis of part of the sample;[8] use of high-potency cannabis (skunk) confers an increased risk of psychosis compared with traditional low-potency cannabis (hash). Additionally, because of the increased sample size in the present study, we were able to combine information on frequency of use and type of cannabis used into a single measure. This combined measure suggested that the strongest predictor of case-control status (ie, predictor of whether a random individual would be case or control) was daily-skunk use. Figure 2, which shows the adjusted ORs for psychotic disorders for each of the composite cannabis exposure measure groups, shows how the ORs for skunk users increase with the frequency of use.

Samples of skunk seized in the London area in 2005,[13] 2008,[14] and more recently, as reported by Freeman and colleagues,[16] contained more THC than did samples of hash, and virtually no cannabidiol. Use of cannabis with a high concentration of THC might have a more detrimental effect on mental health than use of a weaker form. Indeed, in line with epidemiological evidence,[2,3] the results of experimental studies[17,18] that investigated the acute effects of intravenous administration of THC in non-psychotic volunteers showed that the resulting psychotic symptoms were dependent on the dose. Furthermore, the scarcity of cannabidiol in skunk-like cannabis might also be relevant because evidence suggests that cannabidiol ameliorates the psychotogenic effect of THC and might even have antipsychotic properties.[19,20] The presence of cannabidiol might explain our results, which showed that hash users do not have any increase in risk of psychotic disorders compared with non-users, irrespective of their frequency of use. Morgan and colleagues[21] previously reported that, in healthy volunteers who smoked cannabis, individuals with

hair traces of THC and cannabidiol had fewer schizophrenia-like symptoms than those with hair traces of THC only.

In our results, a combined measure of exposure to cannabis, daily use of high-potency cannabis, predicted a greater risk of psychotic disorders than did the single measures of either frequency or potency. However, a simple yes-or-no question of whether people use skunk might be more useful to identify those at increased risk to develop psychosis because of their cannabis use. In view of the high prevalence of skunk use in our study population, if a causal role for cannabis is assumed, skunk use alone was responsible for 24% of those adults presenting with first-episode psychosis to the psychiatric services in south London.

South London has one of the highest recorded incidence rates of psychosis in the UK.[22] Boydell and colleagues[23] showed that the incidence of schizophrenia had doubled since 1965,[24] and that one possible contribution to this was the increase in cannabis use among individuals who developed schizophrenia. In the present study, we identified an increased estimate for the PAF accounted for by cannabis (24%) compared with previous studies, which reported PAFs of 6·2% in Germany,[25] 8% in New Zealand,[26] and 13·3% in Holland.[5] This finding could be caused by, not only the greater use of cannabis, but also the greater use of high-potency (skunk-like) cannabis in south London than in these other countries in earlier periods.[27]

Hickman and colleagues[6] suggested that the number of people who need to be treated to stop their cannabis use to prevent one case of schizophrenia is large, but would become substantially lower if more was understood about which individuals are at greatest risk because of their pattern of use or their susceptibility to psychosis.[6] In relation to susceptibility to schizophrenia, Henquet and colleagues[25] calculated that the PAF for individuals in the general population with a predisposition for psychosis at baseline was more than double (14·2%) that of the total population (6·2%). Our data suggest that the potency of the cannabis used also needs to be taken into account in calculations of the PAF.

The strategy we used for control recruitment, based on a variety of advertising strategies rather than on random selection, might have biased the findings. However, the final sample of controls was similar, according to the last UK census data, to the population from which the cases were drawn. Moreover, rather than this approach undersampling individuals who used cannabis, the proportion of controls with a history of cannabis use (63%) was more than the national average (40%) for similar age groups,[28] showing the high prevalence of cannabis use in south London. Furthermore, if we had oversampled individuals who used cannabis, this oversampling would have caused underestimation of the effects of cannabis use on risk of psychotic disorders.

A theoretical explanation of why skunk might have been preferred by patients with first-episode psychosis is that, when they began to experience their illness prodrome, these individuals might have sought increased concentrations of THC to self-medicate. However, experimental studies show that THC induces psychotic symptoms, while cannabidiol ameliorates them and reduces anxiety.[16–19] That people who already have prodromal symptoms would choose a type of cannabis that is high in THC and has little cannabidiol (such as skunk), which might exacerbate their symptoms, rather than a cannabidiol-containing type (such as hash), would seem counterintuitive.

A possible limitation of our study is the absence of data on number of joints or grams used per day. However, because we collected information about use over a period of years and not about present use, the reliability of such detailed information would probably have been confounded by recall bias to a greater extent than was the general description of pattern of use that we obtained. The fact that we were able to collect detailed information on other environmental factors and control for their potential confounding effects is a key strength of our study.

Our findings show the importance of raising public awareness of the risk associated with use of high-potency cannabis (panel), especially when such varieties of cannabis are becoming more available.[29] The worldwide

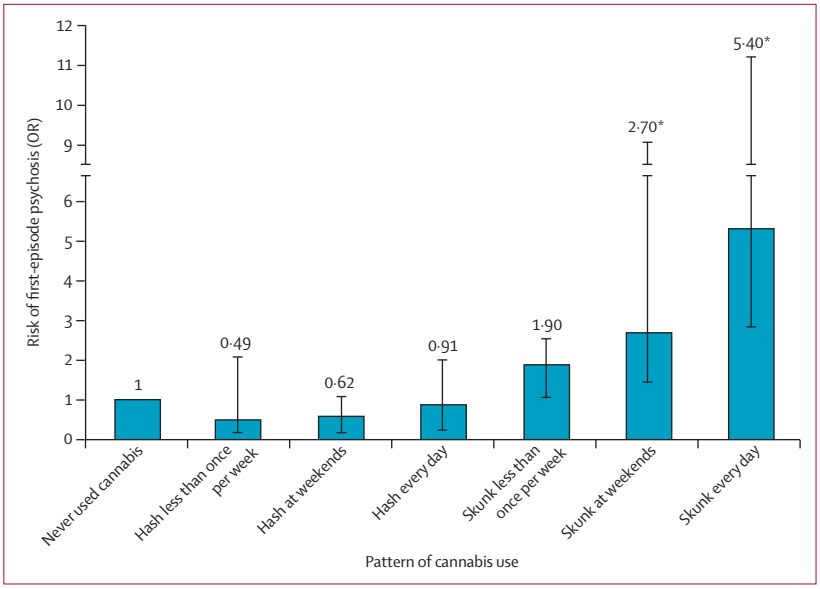


***Figure 2:*** **Probability of individuals having a psychotic disorder by pattern of cannabis use**
OR adjusted for age, gender, ethnic origin, education, employment status, and tobacco use. OR=odds ratio. *p<0·05.

| | Odds ratio* (95% CI) | Prevalence of exposure in patients with first-episode psychosis | Population attributable fraction (95% CI) |
|---|---|---|---|
| Daily cannabis use | 3·04 (1·91–7·76) | 123/410 (30%) | 19·3% (13·1–27·0) |
| Skunk use | 2·91 (1·52–3·60) | 218/410 (53%) | 24·0% (17·4–30·6) |
| Skunk use every day | 5·40 (2·80–11·30) | 103/410 (25%) | 16·0% (14·0–20·3) |

*Adjusted for age, gender, ethnic origin, number of cigarettes, alcohol units, other drugs used, level of education, and employment status.

***Table 4:*** **Population attributable fraction for daily use of cannabis, skunk use, and skunk use every day**

## *Panel:* Research in context

### Systematic review

We searched PubMed for studies that estimated the effect of cannabis use on the number of new cases of psychosis arising in specific populations, using both the terms "population attributable fraction", and "number needed to treat". We also searched for studies that investigated the association between the "high potency and/or skunk" type of cannabis and psychosis. We included all studies available on PubMed until Sept 31, 2014. We identified three studies,[7,8,16] all of which met our inclusion criteria.

### Interpretation

The association between cannabis use and increased risk of developing schizophrenia-like psychosis has been consistently reported by prospective epidemiological studies.[2,3] Our previous study was the first to show that use of high-potency (skunk-like) cannabis carries the highest risk for psychotic disorders.[8] In the present larger sample analysis, we replicated our previous report and showed that the highest probability to suffer a psychotic disorder is in those who are daily users of high potency cannabis. Indeed, skunk use appears to contribute to 24% of cases of first episode psychosis in south London. Our findings show the importance of raising awareness among young people of the risks associated with the use of high-potency cannabis. The need for such public education is emphasised by the worldwide trend of liberalisation of the legal constraints on cannabis and the fact that high potency varieties are becoming much more widely available. Finally, in both primary care and mental health services, a simple yes-or-no question of whether people use skunk might be more useful to identify those at increased risk to develop psychosis because of their cannabis use.

trend of liberalisation of the legal constraints on the use of cannabis further emphasises the urgent need to develop public education to inform young people about the risks of high-potency cannabis.

#### Contributors

In collaboration with the Genetics and Psychosis Study (VM, TRM, SAS, MR, AM, JO'C, CI, PD, CP) and the PUMP study (FG, ZA, PG-S) teams, MDF, AT, and SAS collected the data and MDF prepared the data for the analysis. MDF did the data analysis with CM. MB and FB contributed to the data entry. ML and RMM supervised MDF in the interpretation of the results. EC and SF contributed to the literature review and to the selection of the references. ASD and JP reviewed the manuscript and contributed to its final draft. All authors had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

#### Declaration of interests

RMM reports honoraria from Otsuka, Lundbeck, and Janssen, which he received for lecturing on the report of the Schizophrenia Commission. All other authors declare no competing interests.

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Annals of Internal Medicine REVIEW

# The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms

## A Systematic Review

**Shannon M. Nugent, PhD; Benjamin J. Morasco, PhD; Maya E. O'Neil, PhD; Michele Freeman, MPH; Allison Low, BA; Karli Kondo, PhD; Camille Elven, MD; Bernadette Zakher, MBBS; Makalapua Motu'apuaka, BA; Robin Paynter, MLIS; and Devan Kansagara, MD, MCR**

**Background:** Cannabis is increasingly available for the treatment of chronic pain, yet its efficacy remains uncertain.

**Purpose:** To review the benefits of plant-based cannabis preparations for treating chronic pain in adults and the harms of cannabis use in chronic pain and general adult populations.

**Data Sources:** MEDLINE, Cochrane Database of Systematic Reviews, and several other sources from database inception to March 2017.

**Study Selection:** Intervention trials and observational studies, published in English, involving adults using plant-based cannabis preparations that reported pain, quality of life, or adverse effect outcomes.

**Data Extraction:** Two investigators independently abstracted study characteristics and assessed study quality, and the investigator group graded the overall strength of evidence using standard criteria.

**Data Synthesis:** From 27 chronic pain trials, there is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations. According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is insufficient.

**Limitation:** Few methodologically rigorous trials; the cannabis formulations studied may not reflect commercially available products; and limited applicability to older, chronically ill populations and patients who use cannabis heavily.

**Conclusion:** Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.

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For author affiliations, see end of text.
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The use of medicinal cannabis has become increasingly accepted in the United States and globally (1, 2). Eight states and the District of Columbia have legalized cannabis for recreational purposes, and 28 states and the District of Columbia have legalized it for medical purposes (3). Between 45% and 80% of persons who seek medical cannabis do so for pain management (4, 5). Among patients who are prescribed long-term opioid therapy for pain, up to 39% are also using cannabis (6, 7). Physicians will increasingly need to engage in evidence-based discussions with their patients about the potential benefits and harms of cannabis use. However, little comprehensive and critically appraised information exists about the benefits and harms of using cannabis to treat chronic pain. The objectives of this systematic review were to assess the efficacy of cannabis for treating chronic pain and to provide a broad overview of the short- and long-term physical and mental health effects of cannabis use in chronic pain and general patient populations.

## METHODS

### Topic Development

This article is part of a larger report commissioned by the Veterans Health Administration (8). A protocol describing the review plan was posted to a publicly accessible Web site before the study began (9).

### Data Sources and Searches

We searched MEDLINE, Embase, PubMed, PsycINFO, Evidence-Based Medicine Reviews (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, and Cochrane Central Register of Controlled Trials), and gray literature sources from database inception through February 2016. We updated this search specifically for new randomized controlled trials (RCTs) and systematic reviews in March 2017. We obtained additional articles from systematic reviews, reference lists, and expert recommendations. We also searched for ongoing, unpublished, or re-

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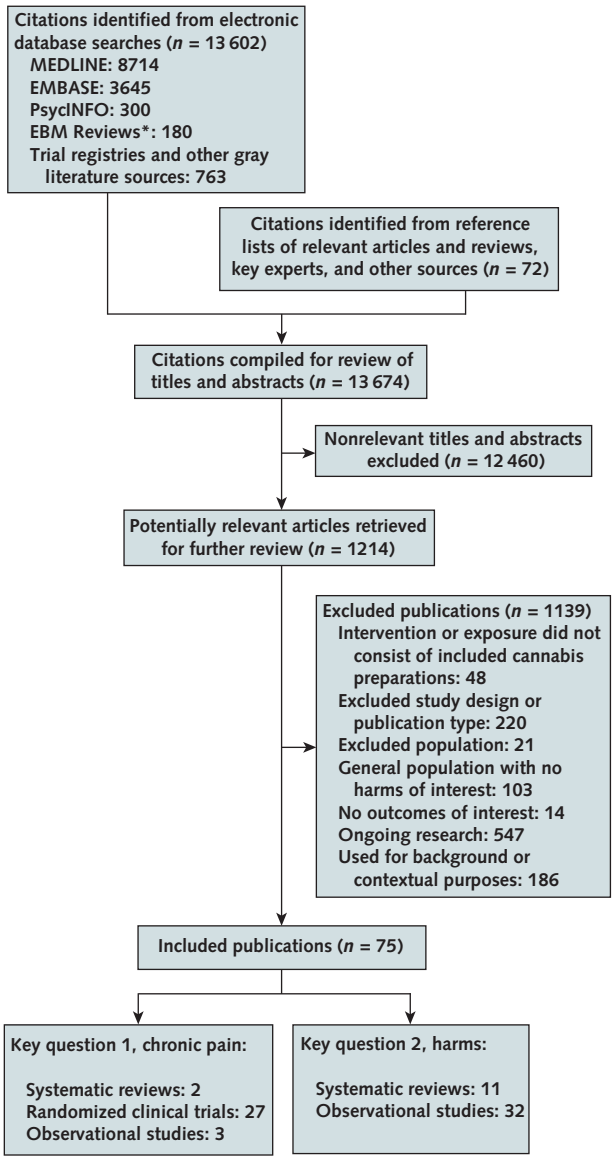
***Figure.*** Literature flow diagram.




* Includes Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, and Cochrane Central Register of Controlled Trials.

cently completed studies on ClinicalTrials.gov, the International Clinical Trials Registry Platform, the ISRCTN Registry, National Institutes of Health RePORTER, and the Agency for Healthcare Research and Quality Grants On-Line Database. Supplement 1 (available at Annals .org) provides details on the search strategy, which we developed in consultation with a research librarian.

## Study Selection

We included English-language studies assessing the effect on nonpregnant adults of plant-based cannabis preparations or whole-plant extracts, such as nabiximols, a nonsynthetic pharmaceutical product with a standard composition and dose (oromucosal spray delivering tetrahydrocannabinol [THC], 2.7 mg, and cannabidiol, 2.5 mg). We did not include synthesized, pharmaceutically prepared cannabinoids, such as dronabinol or nabilone, because they are not available in dispensaries, and the efficacy of synthetic cannabinoid preparations for chronic pain was examined in 2 recent reviews (10, 11). We broadly defined plant-based cannabis preparations to include any preparation of the cannabis plant itself (for example, cannabis cigarettes and oils) or cannabis plant extracts to capture the variety of products available in U.S. dispensaries (12).

To address the efficacy of cannabis for treating chronic pain, we included controlled clinical trials and cohort studies. This review focuses specifically on pain outcomes, although our larger report and search were designed to include other outcomes, such as sleep and quality of life (8). Because data about harms in the general population might be applicable to chronic pain populations, we examined harms broadly and reported whether the data were derived from studies of the general population or populations with chronic pain. To capture potential cannabis-related harms that may be of interest to clinicians and patients, but whose prevalence has not been well-characterized in larger-scale observational studies, we also included case series and descriptive studies of "emerging harms." Supplement 2 provides the criteria we used for study selection.

We searched for primary literature and systematic reviews; we dual-reviewed 5% of identified abstracts and all of the included full-text articles to ensure reliability. Disagreements were resolved by a third reviewer. Given the broad scope of this review, we summarized data from existing systematic reviews. We included only reviews that clearly reported their search strategy, reported inclusion and exclusion criteria, and appraised the internal validity of the included trials (13). We prioritized the most recent reviews and those with the broadest scope. In addition, we included individual studies that met inclusion criteria and either were published after the end search date of the included review or were not included in a prior systematic review.

## Data Extraction and Quality Assessment

For all reports, 2 investigators abstracted details of study design, setting, patient population, intervention, and follow-up, as well as important co-interventions, health outcomes, health care use, and harms.

Two reviewers independently assessed each trial (including those that were identified from a prior systematic review) as having low, high, or unclear risk of bias (ROB) for the pain outcome using a tool developed by the Cochrane Collaboration (14). Disagreements were resolved by consensus. To assess the ROB of observational studies for the pain outcome, we considered potential sources of bias most relevant to this evidence base and adapted existing assessment tools (15, 16) (Supplement 3).

## Data Synthesis and Analysis

For the subgroup of neuropathic pain studies, we did a study-level meta-analysis of the proportion of

patients experiencing clinically significant (≥30%) pain relief (Supplement 4), and we used the profile-likelihood random-effects model (17) to combine risk ratios. We assessed the magnitude of statistical heterogeneity among the studies using the standard Cochran chi-square test, the $I^2$ statistic (18). All analyses were done using Stata/IC, version 13.1 (StataCorp). Clinical heterogeneity, variation in outcomes reported, and the small number of trials precluded meta-analysis for other subgroups and outcomes, so we reported these qualitatively. After group discussion, we classified the overall strength of evidence for each outcome as high, moderate, low, or insufficient on the basis of the consistency, coherence, and applicability of the body of evidence as well as the internal validity of individual studies (19, 20).

### Role of the Funding Source

The U.S. Department of Veterans Affairs Quality Enhancement Research Initiative supported the review but had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication.

## RESULTS

After reviewing 13 674 titles and abstracts, we included 13 systematic reviews and 62 primary studies (Figure). Table 1 provides study-level details and the ROB rating for each of the chronic pain trials. Table 2 summarizes findings, including the ROB rating, by pain subgroup. Table 3 summarizes the harms in both pain and general populations. Supplement 5 provides additional study-level data from pain studies not included in prior reviews and from studies on general harms.

### Effects of Cannabis in Treating Chronic Pain

We identified 22 RCTs (21–42) from 2 recently published systematic reviews (10, 11) and an additional 8 studies (5 RCTs [43–47] and 3 cohort studies [48–50]) that met our inclusion criteria and were not included in prior reviews. The primary methods of continuous pain assessment were a visual analogue scale from 0 to 100 mm and a numerical rating scale (NRS) from 0 to 10 (where 0 indicated no pain and 10 indicated the worst possible pain). Some of the studies identified the proportion of participants who had clinically significant improvements in pain intensity (defined as ≥30% reduction, or approximately 2 points on the NRS and 20 mm on the visual analogue scale).

#### *Neuropathic Pain*

Thirteen trials examined the effects of cannabis-based preparations on neuropathic pain (Table 1). Participants had central or peripheral neuropathic pain related to various health conditions. Of these studies, 11 were rated as having low ROB (24, 27, 28, 30, 31, 33, 36, 39, 40, 43, 47), 1 as having unclear ROB (26), and 1 as having high ROB (35). Overall, we found low-strength evidence that cannabis may alleviate neuropathic pain in some patients (Table 2). Studies generally did not find clinically significant between-group differences on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later. Across 9 studies, intervention patients were more likely to report at least 30% improvement in pain (risk ratio, 1.43 [95% CI, 1.16 to 1.88]; $I^2$ = 38.6%; $P$ = 0.111) (Supplement 4). Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes.

In the largest RCT, 246 patients with peripheral neuropathic pain self-titrated nabiximols up to a maximum dosage of 24 sprays per day or received a placebo (27). Those who completed the study (79 in the nabiximols group and 94 in the placebo group) and responded positively to the intervention had a significant decrease in pain (odds ratio, 1.97 [CI, 1.05 to 3.70]). However, among all participants, including those who did not have an intervention response, the reduction in the NRS pain score did not reach clinical or statistical significance. The second-largest RCT with low ROB included 55 patients with HIV-associated sensory neuropathy who were randomly assigned to smoke either 3.56% THC cigarettes or a placebo 3 times per day for 5 days. Among those who completed the study, 52% ($n$ = 13) of the treatment group had a clinically significant reduction in pain compared with 24% ($n$ = 6) of the placebo group (33).

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]).

#### *Multiple Sclerosis*

Nine trials examined the effects of cannabis-based preparations on pain among patients with multiple sclerosis (MS) (Table 1). Participants generally had intractable body pain or neuropathic pain related to a clinically confirmed diagnosis of MS. Three of these trials were rated as having low ROB (29, 42, 44), 5 as having unclear ROB (22, 37, 38, 41, 45), and 1 as having high ROB (32). Overall, we found insufficient evidence to characterize the effects of cannabis on pain in patients with MS (Table 2) because of the small number of methodologically rigorous studies, inconsistent findings across studies, lack of long-term outcomes, and small number of patients included in the trials.

Of the 3 low-ROB trials, 1 found small but clinically nonsignificant alleviation of pain at 5 weeks, 1 found

***Table 1.*** Characteristics and Findings of RCTs on Cannabis Extracts for Treating Chronic Pain*

| Trial | Pain Type | *N* | Intervention Formulation; Dosage; Study Design | Duration |
|---|---|---|---|---|
| Abrams et al, 2007 (33) | Neuropathic sensory, HIV-associated | 55 | Smoked THC, 4%; 1 cigarette/d (0.9 g) | 12 d |
| Berman et al, 2004 (30) | Neuropathic brachial plexus avulsion | 48 | Nabiximols (THC oromucosal spray); ≤48 sprays/d; crossover | 2 wk (no washout) |
| Ellis et al, 2009 (31) | Neuropathic sensory, HIV-associated | 34 | Smoked THC, started at 4% and adjusted as necessary; 4 smoking sessions/d; crossover | 5 d (2-wk washout) |
| Lynch et al, 2014 (24) | Neuropathic chemotherapy-induced | 18 | Nabiximols; ≤12 sprays/d | 4 wk (2-wk washout) |
| Notcutt et al, 2004 (43) | Mostly neuropathic; 47% MS | 34 | Sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; 1 to 8 sprays/d | 8 wk |
| Nurmikko et al, 2007 (35) | Neuropathic pain with allodynia | 125 | Nabiximols; ≤48 sprays/d | 5 wk |
| Selvarajah et al, 2010 (26) | Neuropathic diabetic peripheral | 30 | Nabiximols; maximum unclear | 12 wk |
| Serpell et al, 2014 (27) | Neuropathic peripheral with allodynia | 246 | Nabiximols; ≤24 sprays/d | 15 wk |
| Wallace et al, 2015 (36) | Neuropathic diabetic peripheral | 16 | Vaporized THC, 7%, 4%, or 1%; 4 h observation at each dose; crossover | 4 h (2-wk washout) |
| Ware et al, 2010 (39) | Neuropathic, postsurgical or posttraumatic | 23 | Smoked THC, 2.5%, 6%, or 9.4%; crossover | 5 d (9-d washout) |
| Wilsey et al, 2008 (28) | Neuropathic | 38 | Smoked THC, 3.5% or 7%; 9 puffs; crossover | 6 h (3- to 21-d washout) |
| Wilsey et al, 2013 (40) | Neuropathic, peripheral | 39 | Vaporized THC, 1.29% or 3.53%; 4 puffs at 1 h after baseline, 4 to 8 puffs at 3 h; crossover | 6 h (3- to 7-d washout) |
| Wilsey et al, 2016 (47) | Neuropathic, spinal cord injury | 42 | Vaporized THC, 2.9% or 6.7%; 400 mg using Foltin Puff Procedure at 8 to 12 puffs over 240 min, adaptable dose design | 8 h |
| Collin et al, 2010 (22) | MS | 337 | Nabiximols; ≤24 sprays/d | 14 wk |
| Corey-Bloom et al, 2012 (37) | MS | 37 | Smoked THC, 4%; one 800-mg cigarette | 3 d (11-d washout) |
| Langford et al, 2013 (41) | MS | 339 | Nabiximols; ≤12 sprays/d | 14 wk |
| Rog et al, 2005 (42) | MS | 66 | Nabiximols; ≤48 sprays/d | 5 wk |
| Van Amerongen et al, 2017 (45) | MS | 24 | Orally ingested THC, 99% (EPC002A, Namisol); 1.5 or 5 mg 3 times/d | 2 wk |
| Wade et al, 2003 (44) | MS (67%) | 24 | Pump-action sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; ≤120 mg/d; crossover | 2 wk (no washout) |
| Wade et al, 2004 (38) | MS | 160 | Nabiximols; ≤48 sprays/d | 6 wk |
| Zajicek et al, 2003 (32) | MS | 657 | THC/CBD capsules; ≤25 mg/d | 15 wk |
| Zajicek et al, 2012 (29) | MS | 279 | THC/CBD capsules; ≤25 mg/d | 12 wk |
| Johnson et al, 2010 (23) | Cancer | 60<br>58 | Nabiximols; ≤48 sprays/d<br>2.7 mg THC oromucosal spray; ≤48 sprays/d | 2 wk<br>2 wk |
| Noyes et al, 1975 (34) | Cancer | 10 | THC capsules; 5, 10, or 15 mg; crossover | 1 d (no washout) |
| Portenoy et al, 2012 (25) | Cancer | 360 | Nabiximols; 1 to 4, 6 to 10, or 11 to 16 sprays/d | 9 wk |
| de Vries et al, 2016 (46) | Abdominal pain (includes chronic pancreatitis, postsurgical pain) | 65 | Orally ingested THC, 99% (EPC002A, Namisol); step-up phase: days 1 to 5, 3 mg 3 times/d; days 6 to 10, 5 mg 3 times/d; stable dose phase: days 11 to 52, 8 mg 3 times/d | 7 wk |
| Blake et al, 2006 (21) | Rheumatoid arthritis | 58 | Nabiximols; ≤48 sprays/d | 5 wk |

C = control; CBD = cannabidiol; MS = multiple sclerosis; NRS = numerical rating scale; NS = not significant; RCT = randomized controlled trial; T = treatment; THC = tetrahydrocannabinol; VAS = visual analogue scale.
* Study findings other than those specified (proportion of patients with ≥30% pain reduction and mean between-group difference in change from baseline in pain score) are not shown.
† NRS score range, 0–10 points
‡ VAS score range, 0–100 mm.

no difference in outcome, and a larger trial found that more intervention patients reported relief from body pain at 12 weeks (28.0% vs. 18.7%; $P = 0.028$) (29).

### *Cancer Pain*

Three trials ($n = 547$) examined the effects of cannabis-based preparations on pain among patients with cancer-related pain (Table 1). Participants had

*Table 1*–Continued

| Patients Achieving ≥30% Pain Reduction, T vs. C, *n/N (%)* | Mean Difference (T − C) in Change From Baseline | | Overall Risk of Bias |
|---|---|---|---|
| | NRS Pain Scale, *points†* | VAS Pain Scale, *mm‡* | |
| 13/25 vs. 6/25 (52.0 vs. 24.0) | – | – | Low |
| – | – | – | Low |
| – | – | – | Low |
| – | – | – | Low |
| THC: 9/24 vs. NR (37.5 vs. NR)<br>CBD: 3/24 vs. NR (12.5 vs. NR)<br>THC+CBD: 9/24 vs. NR (37.5 vs. NR) | – | – | Low |
| 16/63 vs. 9/62 (25.4 vs. 14.5) | – | −8.03 (−13.83 to −2.23) | High |
| 8/15 vs. 9/14 (53.3 vs. 64.3) | – | 9.50 (−11.30 to 27.80) | Unclear |
| 34/123 vs. 19/117 (27.6 vs. 16.2) | −0.34 (−0.79 to 0.11) | −2.86 (−7.22 to 1.50) | Low |
| 1% THC: 10/16 vs. 10/16 (62.5 vs. 62.5)<br>4% THC: 12/16 vs. 10/16 (75.0 vs. 62.5)<br>7% THC: 13/16 vs. 10/16 (81.3 vs. 62.5) | – | – | Low |
| – | – | – | Low |
| 3.5% THC: 4/36 vs. 2/33 (11.1 vs. 6.1)<br>7% THC: 0/34 vs. 2/33 (0.0 vs. 6.1) | – | – | Low |
| 1.29% THC: 21/37 vs. 10/38 (56.8 vs. 26.3)<br>3.53% THC: 22/36 vs. 10/38 (61.1 vs. 26.3) | – | 1.29% THC: −11<br>3.53% THC: −10 | Low |
| 2.9% THC: 18/26 vs. 8/18 (69.2 vs. 44.4)<br>6.7% THC: 31/35 vs. 8/18 (88.6 vs. 44.4) | – | – | Low |
| – | – | – | Unclear |
| – | – | – | Unclear |
| 84/167 vs. 77/172 (50.3 vs. 44.8) | 0.17 (−0.62 to 0.29) | – | Unclear |
| – | −1.25 (−2.11 to −0.39) | −6.58 (−12.97 to −0.19) | Low |
| – | Week 2: −1.09 (−1.98 to −0.20) ($P$ = 0.018)<br>Week 4: −0.85 (−1.74 to −0.04) ($P$ = 0.061) | – | Unclear |
| – | – | Baseline: 30.1 (SD, 17.8)<br>2nd week of each group:<br>CBD: 54.8 (SD, 22.6; $P$ < 0.05)<br>THC: 54.6 (SD, 27.4; $P$ < 0.05)<br>THC+CBD: 51.3 (SD, 27.0; $P$ = NS)<br>Placebo: 44.5 (SD, 22.7) | Low |
| – | – | – | Unclear |
| – | – | – | High |
| – | – | – | Low |
| 23/53 vs. 12/56 (43.4 vs. 21.4)<br>12/52 vs. 12/56 (23.1 vs. 21.4) | −0.32 (−0.86 to 0.22)<br>−0.67 (−1.21 to −0.14) | – | Unclear |
| – | – | – | High |
| 1 to 4 sprays: 30/91 vs. 24/91 (33.0 vs. 26.4)<br>6 to 10 sprays: 26/87 vs. 24/91 (29.9 vs. 26.4)<br>11 to 16 sprays: 22/90 vs. 24/91 (24.4 vs. 26.4) | 1 to 4 sprays: −0.75 (−1.28 to −0.22)<br>6 to 10 sprays: −0.36 (−0.89 to 0.18)<br>11 to 16 sprays: −0.09 (−0.62 to 0.44) | – | Unclear |
| – | −1.6 (SD, 1.78) vs. −1.9 (SD, 2.18) ($P$ = 0.92) | – | High |
| – | – | −3 (−18 to 9) | Unclear |

moderate to severe intractable pain related to a clinically confirmed diagnosis of cancer, although the exact cause of pain was unspecified. Two studies were rated as having unclear ROB (23, 25), and 1 study was rated as having high ROB (34). Overall, these trials provide insufficient evidence because of the small number of studies and their methodological limitations, including high attrition, exclusion of patients with variable pain

scores, use of some nonvalidated measures, and lack of clarity about randomization and blinding procedures (Table 2).

#### *Other or Mixed Pain Conditions*

Two trials (21, 46) and 3 cohort studies (48–50) examined the effects of cannabis-based preparations on pain among patients with other or mixed pain conditions, including fibromyalgia, rheumatoid arthritis, and inflammatory abdominal pain (Table 1). One trial was rated as having unclear ROB (21), and 1 was rated as having high ROB (46). One observational study was rated as having low ROB (50), and the other 2 were at high ROB (48, 49). Overall, evidence was insufficient because of the inconsistent results and the paucity of methodologically rigorous studies (Table 2). Limitations of individual studies include lack of follow-up, inadequate allocation concealment, selection bias, high attrition, and lack of inclusion of nonnaive cannabis users.

### Harms of Cannabis Use

#### *General Adverse Events Among Patients With Chronic Pain*

Data from 2 systematic reviews examining cannabis for chronic pain suggest that cannabis use may be associated with a higher risk for short-term adverse effects (10, 11). However, the rates of adverse events did not significantly differ between groups in the additional pain trials we reviewed. Although most reported adverse events were mild, such as dizziness and lightheadedness, some were serious, such as suicide attempts, paranoia, and agitation (Table 3). An additional prospective observational study did not detect a difference in serious adverse events between a cannabis group (12.5% ± 1.5% THC, 2.5 g/d) and control group (adjusted incidence rate ratio for event, 1.08 [CI, 0.57 to 2.04]) (50).

#### *Medical Harms in the General Population*

Moderate-strength evidence from 2 well-designed cohort studies (52, 53) suggests that low levels of cannabis smoking do not adversely affect lung function over about 20 years in young adults, but some evidence suggests that daily use may cause adverse pulmonary effects over an extended period (Table 3). Because of methodological limitations, including a lack of longitudinal exposure measurement and potential recall bias, 2 studies (55, 56) give insufficient evidence about the effect of cannabis use on the risk for cardiovascular events. A meta-analysis (59) of 9 case–control studies provides low-strength evidence that cannabis use is not associated with an increased risk for head and neck cancer (odds ratio, 1.02 [CI, 0.91 to 1.14]). Another meta-analysis (57) of 6 case–control studies provides low-strength evidence of no elevated risk for lung cancer with cannabis use (odds ratio, 0.96 [CI, 0.66 to 1.38]). Insufficient evidence exists about the effects of cannabis on testicular (60) or transitional cell cancer (61) (Table 3).

#### *Mental Health and Cognitive Harms in the General Population*

One systematic review (64) and 8 studies (65–71, 74) consistently found an association between cannabis use (specifically related to THC content) and the development of psychotic symptoms (low strength of evidence) (Table 3). The association was seen both in populations at risk for psychotic spectrum disorders and in average-risk populations. The possibility that cannabis contributes directly to the development of psychotic symptoms is supported but not proved by biological plausibility, evidence of a dose–response relationship, prospective cohort studies, and small experimental studies.

A systematic review of 6 longitudinal studies provides low-strength evidence of an association between cannabis use and exacerbation of manic symptoms in patients with known bipolar disorder. The review found higher incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder (pooled odds ratio, 2.97 [CI, 1.80 to 4.90]) (63).

Two systematic reviews of studies in general populations provide moderate-strength evidence that active, long-term cannabis use is associated with small to moderate negative effects on many domains of cognitive function, but evidence on cognitive effects in past users is insufficient (72, 73).

A meta-analysis of 4 epidemiologic studies found significantly increased odds of suicide death (pooled odds ratio, 2.56 [CI, 1.25 to 5.27]) with any cannabis use. However, our confidence in the findings is limited by inconsistent findings among included studies, inadequate assessment of exposure, and inadequate adjustment for confounding among the studies (insufficient strength of evidence) (62, 64).

#### *Motor Vehicle Accidents in the General Population*

Moderate-strength evidence from a recent meta-analysis of 21 multinational observational studies suggests that acute cannabis intoxication is associated with a moderate increase in collision risk (odds ratio, 1.35 [CI, 1.15 to 1.61]) (51).

#### *Other Harms in the General Population*

Long-term cannabis use has been associated with a severe form of cyclic vomiting called cannabinoid hyperemesis syndrome (75–82). Serious infectious diseases, including aspergillosis (83–86) and tuberculosis, have also been associated with smoking cannabis (87, 88). Evidence of the effects of cannabis on violent behavior is mixed (89, 90). Cannabis use was associated with incident cannabis use disorder (adjusted odds ratio, 9.5 [CI, 6.4 to 14.1]) in a large ($N$ = 34 653) prospective cohort study (91). In a cross-sectional study of patients receiving daily opioid therapy for chronic pain, the prevalence of cannabis use disorder was 2.4%, and 13.2% reported having used cannabis in the past 30 days. The prevalence of cannabis use disorder among the subgroup of current users, however, was not reported (92).

## DISCUSSION

In our systematic review, we found limited evidence on the potential benefits and harms of cannabis use in chronic pain populations (Tables 2 and 3). We found low-strength evidence that cannabis preparations with precisely defined THC–cannabidiol content (most in a 1:1 to 2:1 ratio) may alleviate neuropathic pain but insufficient evidence in populations with other types of pain. Most studies are small, many have methodological flaws, and the long-term effects are unclear given the brief follow-up of most studies.

Among neuropathic pain studies, we found a discrepancy between continuous and dichotomous pain outcomes. Possible interpretations are that cannabis is simply not consistently effective or that, although cannabis may not have clinically important effects on average, subgroups of patients may experience large effects. We did not find data to clarify which subgroups of patients are more or less likely to benefit.

Our findings complement several recent reviews. In 1 review, the authors concluded that low- to moderate-strength evidence supports the efficacy of cannabis in chronic pain populations, limited mainly to those with MS or neuropathic pain. However, a separate group reviewed and reanalyzed a similar set of published articles and determined that insufficient to low-strength evidence supports the use of cannabis to treat chronic noncancer pain (11). A recent report from the National Academies of Sciences, Engineering, and Medicine examined the biological and clinical effects of cannabis across a broad range of indications and concluded that there is substantial evidence of benefit for patients with

***Table 2.*** Summary of Evidence of the Benefits of Cannabis in Populations With Chronic Pain

| Pain Type | Studies | Findings | Strength of Evidence* | Comments |
|---|---|---|---|---|
| Neuropathic | 11 low-ROB studies; combined *N* = 593:<br>4 of smoked THC (28, 31, 33, 39); combined *N* = 150<br>3 of vaporized THC (36, 40, 47); combined *N* = 97<br>3 of nabiximols (24, 27, 42); combined *N* = 312<br>1 of oromucosal spray delivering THC or THC+CBD (43); *N* = 34<br>1 unclear-ROB study of nabiximols (26); *N* = 30<br>1 high-ROB trial (35); *N* = 125 | Studies did not find a clinically significant between-group difference on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later<br>In a meta-analysis of 9 studies, intervention patients were more likely to report ≥30% improvement in pain (combined RR, 1.43 [95% CI, 1.16–1.88]; $I^2$ = 38.6%; *P* = 0.111) | Low | Few patients enrolled in most low-ROB studies; inconsistent results; marked differences among studies in dosing and delivery mechanism; brevity of study duration; low applicability to formulations available in dispensaries |
| MS | 3 low-ROB trials; combined *N* = 369; 24–279 per study:<br>1 of THC/CBD capsules (29)<br>1 of nabiximols (42)<br>1 of sublingual spray delivering THC, CBD, or THC+CBD (44)<br>5 unclear-ROB trials; combined *N* = 897; 24–339 per study:<br>3 of nabiximols (22, 38, 41)<br>1 of smoked THC (37)<br>1 of orally ingested THC (EPC002A) (45)<br>1 high-ROB trial of THC/CBD capsules (32), *N* = 657 | No consistent clinically significant effects on pain | Insufficient | Few methodologically rigorous studies; inconsistent results; little long-term data; inclusion of pain as a secondary outcome; low applicability to formulations available in dispensaries |
| Cancer | 2 unclear-ROB trials; combined *N* = 596; 177–360 per study:<br>1 of nabiximols (25)<br>1 of nabiximols and THC oromucosal spray in separate groups (23)<br>1 high-ROB trial of THC capsules (34), *N* = 10 | No consistent clinically significant effects on pain | Insufficient | Small number of studies; methodological flaws, including high attrition, lack of clarity about randomization and blinding procedures, and use of nonstandard outcome measures |
| Other/mixed | 1 unclear-ROB trial of nabiximols for rheumatoid arthritis (21); *N* = 58<br>1 high-ROB trial of EPC002A (orally ingested 99% THC) for abdominal pain (46); *N* = 65<br>3 cohort studies of mixed forms of cannabis (smoked, orally ingested, vaporized) for fibromyalgia (48), inflammatory bowel disease/Crohn disease (49), and nociceptive and/or neuropathic pain (50) | Small improvements in pain | Insufficient | Larger observational study had high attrition |

CBD = cannabidiol; MS = multiple sclerosis; ROB = risk of bias; RR = risk ratio; THC = tetrahydrocannabinol.
* Based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows: high = further research is very unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; insufficient = any estimate of effect is very uncertain.

chronic pain. Although the overall conclusions seem to differ from our findings, the authors stipulated that the clinical improvements were modest and limited to neuropathic pain (93), and they underscored the urgent need for better research clarifying the effects of cannabis. Our review augments this report by using a systematic approach on a more focused topic (chronic pain and harms) as well as standard terminology for describing the strength of the body of evidence (19).

Even though we did not find strong, consistent evidence of benefit, clinicians will still need to engage in evidence-based discussions with patients managing chronic pain who are using or requesting to use cannabis. Therefore, clinicians must understand what is known and unknown about its potential harms.

We found moderate-strength evidence that light to moderate cannabis smoking does not adversely affect lung function over about 20 years. However, the limited data on the effects of heavy use suggest a possible deleterious effect on lung function over time (52, 53). We found low-strength evidence that light to moderate cannabis use is not associated with lung cancer or head and neck cancer diagnoses independent of tobacco use, but the data are limited to case–control studies and do not address heavy use. We found insufficient evidence examining whether cannabis use is associated with cardiovascular events over the long term.

Cannabis use has potentially serious mental health and adverse cognitive effects, although data are insufficient to characterize the magnitude of risk or in whom the risk is highest. Cannabis seems to be associated with at least small, short-term deleterious effects on cognition in active users, but long-term effects in past users are uncertain. We found a consistent association between cannabis use and the development of psychotic symptoms over the short and long term. A large prospective cohort study in the United States found that cannabis use was associated with a substantial risk for incident cannabis use disorder and a smaller risk for incident alcohol and other substance use disorders (91). Finally, we found some adverse effects that seem to be related to cannabis use and are important for clinicians to know (for example, infectious disease complications, cannabis hyperemesis syndrome, and violent behavior), but the incidence of these effects has not been well-characterized.

Evidence-based nonpharmacologic and nonopioid pharmacologic therapies are the preferred initial methods for treating chronic pain (94). Clinicians may struggle with treating chronic pain in patients who have not responded to first-line treatment, and cannabis may be perceived as a safer strategy in these patients (95). The scale and severity of adverse events, including death, seen with opioids have not been described with cannabis in the literature (although less research is available on cannabis than on opioids) (95). However, no studies have directly compared cannabis with opioids, and no good-quality data exist on how cannabis use affects opioid use and opioid-related adverse effects. Cross-sectional studies suggest an association between co-occurring cannabis use and adverse opioid-related events (that is, misuse or more refills) among patients prescribed opioids (6, 7, 96–98). By contrast, an open-label study found that pain scores and opioid use decreased over 6 months in participants with chronic pain who initiated cannabis treatment, although confidence in the findings is limited by the large number of participants lost to follow-up (99).

The applicability of study data to current practice is limited in several ways. The patient populations in many studies were highly selected, and some studies included a run-in period after which patients who did not respond were excluded from further study. The data on effectiveness largely come from trials examining formulations with precisely defined THC and cannabidiol content, which differs from the reality of clinical practice. Even though dispensaries are increasingly labeling products' content, discrepancies often exist between labeled and measured content (100). Moreover, the dose of THC assessed in many of the studies is substantially lower than that in products commonly available in dispensaries (for example, 2.5 mg of THC vs. a range of 15 to 200 mg) (100).

Finally, the evidence base on harms is limited because studies include relatively few patients who are older, are chronically ill, or have a history of heavy and prolonged cannabis use. In observational studies, the exact dose of exposure to cannabis was rarely known because of recall bias, and the potency (that is, in estimates of cannabis cigarettes smoked per day) was impossible to assess. On the other hand, this imprecision probably mirrors the uncertainty clinicians will face in discussing benefits and harms with their patients.

Our approach to synthesizing the literature also has limitations. Given the broad scope of our review, we relied on existing systematic reviews to identify the best available evidence. However, we also comprehensively searched for and included newer primary studies, included only good-quality systematic reviews, and reassessed the quality of primary pain studies included in prior reviews. We excluded studies of synthetic prescription cannabinoids, in part because these were included in recent reviews and are not available in cannabis dispensaries. Regardless, inclusion of these studies would not have changed our overall findings because so few studies were available, they were methodologically flawed, and they had very small sample sizes. We examined harms in both chronic pain and general populations, although the degree to which harms data in general populations apply to patients with chronic pain is uncertain. Finally, we focused specifically on pain outcomes in patients with chronic pain, but we acknowledge that other outcomes are also important in the treatment of chronic pain. In our larger report, we describe low-strength evidence that cannabis may reduce spasticity and improve sleep in patients with MS. We found insufficient evidence regarding the effects of cannabis on these outcomes in other patient populations and regarding effects on quality of life and functional status in any population (8).

Virtually no conclusive information exists about the benefits of cannabis in chronic pain populations, and

limited information is available on harms, so methodologically strong research in almost any area is likely to add to the strength of evidence (see **Table 8** of **Supplement 5** for a list of important research gaps and **Table 9** of **Supplement 5** for a list of ongoing studies). Of note, many of the studies we found were done in European countries, suggesting that there may be fewer barriers to conducting cannabis-related research there than in the United States, where barriers are substantial.

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

***Table 3.*** Summary of Evidence for the Harms of Cannabis in Chronic Pain and General Adult Populations

| Outcome | Studies | Findings | Strength of Evidence* | Comments |
|---|---|---|---|---|
| General AEs | 2 systematic reviews (10, 11) and 1 observational study of chronic pain (50) | Cannabis-based treatments associated with higher overall risk for short-term, nonserious AEs. | – | Consistent findings except for serious AE |
| Motor vehicle accidents | Meta-analysis (51) of 21 observational studies; combined *N* = 239 739 | Increase in collision risk (OR, 1.35 [95% CI, 1.15–1.61]). | Moderate | Small but significant increase in risk seen consistently across numerous sensitivity analyses and after adjustment in meta-regression analyses |
| Medical AEs | | | | |
| Pulmonary function | 2 low-ROB prospective cohort studies (52, 53) with 20–32 y follow-up; combined *N* = 6053<br>1 systematic review (54) of 5 observational studies (3 cohort, 2 cross-sectional); combined *N* = 851 | In young adults, low levels of cannabis smoking did not adversely affect lung function over about 20 y<br>A previous meta-analysis of 5 studies found no increased risk for pulmonary adverse effects (OR, 0.80 [95% CI, 0.46–1.39]) | Young adults: moderate<br>Older adults: no evidence | 2 well-done prospective cohort studies, but limited information about effects of heavy use and no information in older or multimorbid populations |
| Cardiovascular effects | 2 high-ROB observational studies: 1 case–crossover (55), *N* = 3882; 1 cohort (56), *N* = 2097 | Cannabis use at time of MI not associated with mortality after mean 12.7-y follow-up, but longitudinal use not assessed<br>Risk of MI within 1 h of cannabis use significantly elevated compared with periods of nonuse, but finding may be inflated by recall bias (OR, 4.8 [95% CI, 2.9–9.5]) | Insufficient | Recall bias; inadequate controlling for confounders; lack of longitudinal exposure data |
| Lung cancer | 1 patient-level meta-analysis (57) of 6 case–control studies; combined *N* = 2150<br>1 high-ROB cohort study (58); *N* = 49 231 | Meta-analysis found no association between light cannabis use and lung cancer | Low | Recall bias; mostly light users, few heavy users; large cohort study had no information about exposure over time |
| Head/neck/oral cancer | Meta-analysis (59) of 9 case–control studies; combined *N* = 5732 | No association between cannabis use and cancer (OR, 1.02 [95% CI, 0.91–1.14]); generally consistent across studies and no evidence of dose-response | Low | Imprecise exposure measurement with potential recall bias; ever-use among studies ranged from 1%–83% |
| Testicular cancer | Meta-analysis (60) of 3 high-ROB case–control studies; combined *N* = 719 | Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer (OR, 1.92 [95% CI, 1.35–2.72]) | Insufficient | Potential confounding from recall bias and tobacco use |
| Transitional cell cancer | 1 high-ROB VA case–control study (61); *N* = 52 | Risk of cancer with >40 joint-years cannabis use vs. none (OR, 3.4; unadjusted *P* = 0.012). | Insufficient | 1 very small case–control study with several methodological flaws |
| Mental health AEs | | | | |
| Suicidal behaviors | 1 meta-analysis (62) of 4 observational studies | Significantly increased odds of suicide with any cannabis use (OR, 2.56 [95% CI, 1.25–5.27]) | Insufficient | Inconsistent results; inadequate exposure ascertainment and adjustment for confounding |
| Mania | 1 meta-analysis (63) of 2 prospective studies | Increased incidence of new-onset mania symptoms among populations without diagnosis of bipolar disorder (OR, 2.97 [95% CI, 1.80–4.90]) | Low | Small number of studies; exposure not well-characterized in 1 study, but other was large community-based cohort study also showing dose–response effect |
| Psychosis | 1 systematic review (64)<br>8 studies (65-71, 74) including patients without psychotic symptoms at baseline: 3 low ROB, 3 medium ROB, 2 high ROB | History of cannabis use associated with increased risk for psychotic symptoms | Low | Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain populations |
| Cognitive effects | 2 systematic reviews (72, 73) | Active long-term cannabis use associated with small negative effects on all aspects of cognition<br>Mixed, inconsistent findings on long-term effects in past users. | Moderate<br>Insufficient (past use) | Consistent data from large number of studies on effects on active long-term use, but inconsistent findings from smaller number of studies regarding effects in those who abstained and no data available specifically in chronic pain populations |

AE = adverse effect; MI = myocardial infarction; OR = odds ratio; ROB = risk of bias; VA = U.S. Department of Veterans Affairs.
* Based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows: high = further research is very unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; insufficient = any estimate of effect is very uncertain.

populations is insufficient. Evidence is also limited on its association with an increased risk for nonserious short-term adverse effects and potentially serious mental health adverse effects, such as psychosis.

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Review

# Cannabis use and mania symptoms: A systematic review and meta-analysis

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ABSTRACT

*Background:* Whilst cannabis use appears to be a causal risk factor for the development of schizophrenia-related psychosis, associations with mania remain relatively unknown. This review aimed to examine the impact of cannabis use on the incidence of manic symptoms and on their occurrence in those with pre-existing bipolar disorder.

*Methods:* A systematic review of the scientific literature using the PRISMA guidelines. PsychINFO, Cochrane, Scopus, Embase and MEDLINE databases were searched for prospective studies.

*Results:* Six articles met inclusion criteria. These sampled 2391 individuals who had experienced mania symptoms. The mean length of follow up was 3.9 years.

Studies support an association between cannabis use and the exacerbation of manic symptoms in those with previously diagnosed bipolar disorder. Furthermore, a meta-analysis of two studies suggests that cannabis use is associated with an approximately 3-fold (Odds Ratio: 2.97; 95% CI: 1.80–4.90) increased risk for the new onset of manic symptoms.

*Limitations:* We were only able to identify a small number of studies of variable quality, thus our conclusions remain preliminary.

*Conclusions:* Our findings whilst tentative, suggest that cannabis use may worsen the occurrence of manic symptoms in those diagnosed with bipolar disorder, and may also act as a causal risk factor in the incidence of manic symptoms. This underscores the importance of discouraging cannabis use among youth and those with bipolar disorder to help prevent chronic psychiatric morbidity. More high quality prospective studies are required to fully elucidate how cannabis use may contribute to the development of mania over time.



**Contents**



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## 1. Introduction

Cannabis is the most commonly used illegal substance in many countries, including the UK (British Crime Survey, 2012) and the USA (NSDUH, 2011). Cannabis use has been shown to produce transient, usually mild, psychotic and affective experiences in healthy individuals (D'souza et al., 2004). Symptoms which persist beyond, or occur independently of, intoxication effects are of greater concern (Moore et al., 2007). There is strong evidence that cannabis use contributes to the development of psychosis and results in a poorer prognosis for those with a pre-existing vulnerability to psychosis (Arseneault et al., 2004; Van Os et al., 2002; Large et al., 2011; Smit et al., 2004). What is less clear is whether cannabis use may also play a causal role in the development of manic affective symptoms and manic episodes specifically (Van Laar et al., 2007; Gruber et al., 2012). Although co-morbid cannabis use is more common in people experiencing bipolar disorder, the association between cannabis use and mania has not received the same degree of attention as that of cannabis use and schizophrenia (Henquet et al., 2006).

Bipolar disorder has the highest rate of substance use co-morbidity of any Axis I disorder (Leweke and Koethe, 2008) and a complex and somewhat reciprocal association between cannabis use and bipolar disorder has been noted (Duffy et al., 2012; Salloum and Thase, 2000). Anecdotal evidence suggests that bipolar patients may engage in 'self-medication' by using cannabis to moderate the symptoms of their illness (Grinspoon and Bakalar, 1998). Other studies indicate that cannabis use predates the advent of bipolar disorder and the reoccurrence of manic episodes (Strakowski et al., 1998; Strakowski and Delbello, 2000), which would suggest a potential causal association.

Bipolar disorder is a complex disease with extensive and diverse symptom clusters (van Rossum et al., 2009) including manic and depressive phases. In terms of cannabis use, associations with manic phases appear especially likely (Strakowski and Delbello, 2000; Sarkar et al., 2003). Manic symptoms are common in patients diagnosed with schizophrenia, and psychotic symptoms often occur in those with bipolar disorder (Dunayevich and Keck, 2000; Henquet et al., 2006). It has been suggested that mania and psychosis may share aetiological influences (e.g., cannabis use, and neuroticism) potentially underpinned by similar physiological mechanisms (Murray et al., 2004). For example, 'sensitisation' of the dopamine system may not only increase the risk of schizophrenia but also mania (Henquet et al., 2006); whether risk eventuates in psychotic or manic disorder is likely to depend on interactions between genetic vulnerability and environmental risk factors (Murray et al., 2004).

Due to the potentially overlapping aetiology between disorders, it is important to distinguish mania from co-occurring psychotic symptoms when assessing associations between cannabis use and mania symptoms. The aim of this review is to assess the prospective associations between cannabis use and mania symptoms as distinct from psychosis symptoms. Specifically we consider:

(1) Does cannabis use lead to increased occurrence of mania symptoms or manic episodes in individuals with pre-existing bipolar disorder?
(2) Does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?

## 2. Method

### 2.1. Search strategy

We used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009) as a framework for our review and reporting procedures. An extensive search of papers in the English language catalogued in PsychINFO, Cochrane, Scopus, Embase and MEDLINE data bases was conducted in June 2014. Search terms were used in three groups and included: cannabis, marijuana, delta-9-tetrahydrocannabinal, cannabinoids, cannabidiol, cannabinol, tetrahydrocannabivarin (group 1) AND bipolar disorder, manic depressive disorder, mania, hypomania, manic depression, bipolar spectrum (group 2) AND onset, trigger, induce,* course (group 3). All MeSH terms (terms related to individual words) were also included within the search. In addition we examined the first 20 pages in Google Scholar using the terms 'cannabis AND cause AND mania'.

### 2.2. Inclusion and exclusion criteria

Studies were included if they were primary experimental, prospective, cohort, or longitudinal and if participants were diagnosed with bipolar disorder I or II (i.e., to explore prospective associations between cannabis use and mania in those with pre-existing bipolar disorder) or described as experiencing mania during the follow-up period (i.e., to explore whether cannabis use precedes the onset of mania in those without pre-existing illness). We included studies reporting on both sub-clinical mania symptoms and manic episodes (i.e., meeting criteria for a full manic episode).We selected *prospective* studies only so we could be more confident regarding the temporal ordering of exposure and outcome variables (Schünemann et al., 2011). Studies with participants primarily diagnosed with a psychotic disorder (e.g., schizophrenia, schizoaffective disorder) were excluded in order to help delineate potential causal associations between

cannabis use and incident mania or mania symptoms/episodes in bipolar disorder specifically (i.e., if participants had a psychotic disorder, associations between cannabis use and mania independent of psychotic symptoms could not be assessed). Non-English papers and articles published before 1980 were also excluded.

### 2.3. Data extraction

Following the initial search, the reference lists of review papers were scrutinised for further relevant studies and a hand search was carried out of articles published over the last five years from six journals *(Acta Psychiatrica Scandinavica, Bipolar Disorders, Journal of Affective Disorders, The British Medical Journal, British Journal of Psychiatry and Psychological Medicine)* previously found to contain a substantial quantity of relevant papers or particularly significant ones. Search results were downloaded into *EndNote X5*. Titles of papers were inspected and excluded if irrelevant. M.G and E.G independently coded 100% of the remaining abstracts applying the inclusion criteria for full text retrieval. Percentage agreement between raters was very high (99%). The researchers met to review discrepancies regarding three papers, which were related to whether the study design met criteria for full text retrieval. If there was doubt over whether an abstract should be included for full text retrieval, the decision was made to include. All papers were read, and if suitable, data was extracted on sample size, study design, sampling frame, length of follow up period, prevalence of cannabis use, other drug use, prevalence of mania/manic symptoms, diagnostic tools used and effect sizes of associations between cannabis and mania/manic symptoms. The main reasons for study exclusion subsequent to full text retrieval were: the mania sample was not clearly defined or outcome was conflated with psychosis, schizophrenia or other mood disorders; cannabis use alone was not clearly defined or was conflated with other drug and alcohol use; or the study design was not prospective.

### 2.4. Quality assessment

The Cochrane collaborations guidelines to assessing risk of bias were used to determine the quality of the studies (Higgins and Altman, 2008). This is a two part tool addressing the seven specific domains of: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. Each domain in the tool includes one or more specific entries in a 'risk of bias' table. Within each entry, the first part of the tool describes what was reported to have happened in the study in sufficient detail to support a judgment relating to the risk of bias. The second part of the tool assigns a judgment relating to the risk of bias for that entry. This is achieved by assigning a judgment of 'Low risk', 'High risk' or 'Unclear risk' of bias.

### 2.5. Data synthesis

In line with the nature of the data extracted, we utilised two methods to synthesise results. Studies regarding aim one (i.e., does cannabis use lead to increased mania symptoms or manic episodes in individuals with pre-existing bipolar disorder?) were synthesised narratively as they did not yield quantitative summary statistics which could be meaningfully combined. Two (of the three) studies pertaining to aim two (i.e., does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?) yielded odds ratios, which could be combined using meta-analysis. Due to the heterogeneity of the studies we decided to use a random effects model (Field and Gillett, 2010) and data was analysed using the *–metan-* command in STATA 12 (for MAC).

## 3. Results

### 3.1. Description of studies

Our initial search identified 781 abstracts. After repeats were excluded, 431 abstracts remained. Three further relevant articles were identified by hand search. All abstracts were read, 33 of which were selected for full text retrieval. Overall, 6 studies met full criteria for inclusion and final data extraction. A PRISMA flowchart describing the results of the search is shown in Fig. 1. The mean length of follow up was 3.9 years. Attrition rates in the included studies ranged from 4% to 49% (2 of the studies (Strakowski et al., 2000; Duffy et al., 2012) did not state attrition rates). Details of the included studies are shown in Table 1. The 6 identified studies comprised a mix of large community (Henquet et al., 2006) ($N=4815$) and clinical (van Rossum et al., 2009) ($N=1612$) populations; moderate community (Tijssen et al., 2010) ($N=705$) and clinical (2008) ($N=166$) populations; one small clinical sample (Strakowski et al., 2000) ($N=50$); and one moderate sample of a high risk population (Duffy et al., 2012) ($N=211$). In total, 14,918 participants were included in the 6 studies.

### 3.2. Quality assessment of studies

Using the Cochrane guidelines to assess risk of bias, no studies were deemed to be low risk of bias in all 7 domains (see Table 2 for risk allocations). A detailed table showing supporting arguments for each of these judgements is available from the authors on request. In Henquet et al. (2006) high risk of bias was evident in selection (inadequate randomisation and concealment of allocation), performance, detection and attrition domains. From an initial 7076 participants, 4815 were included in the final analysis, though the sensitivity analyses suggested that drop-out did not bias study findings. Similarly, in Strakowski and Delbello (2000) there was deemed high risk of bias in selection (random generation and allocation concealment), performance, detection and attrition (rates of attrition not reported) domains. In Tijssen et al. (2010) there was high risk of bias in selection, attrition and 'other' domains. From an initial 1395 participants, only 705 remained at 8 year follow-up.

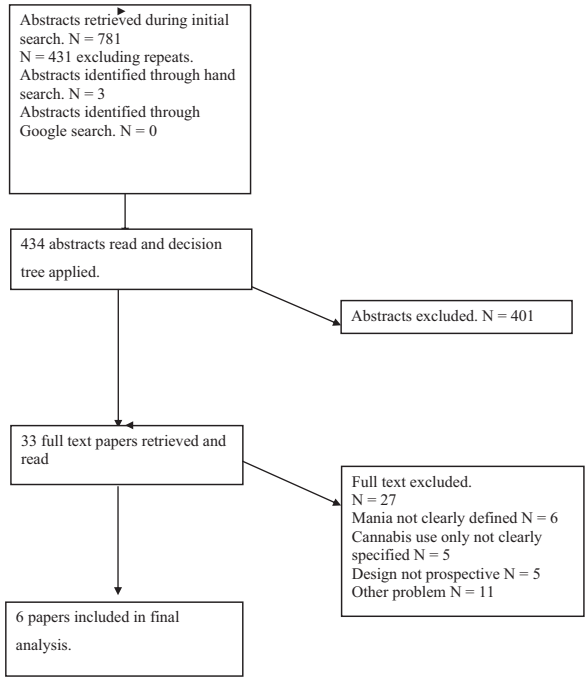


**Fig. 1.** PRISMA flow chart detailing selection of the individual studies.

**Table 1**
Details of studies reporting on cannabis use and mania symptoms.

| Study | Study design, year of enrolment | Participants | Follow-up | Outcome n (%) | Assessments | Diagnostic criteria/ instrument | Definition of cannabis use | Cannabis *N* (%) | Association between cannabis use and mania outcome | Confounding variables controlled for | Limitations of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baethge et al. (2008) | Prospective follow-up, 1989–1996 | 166 first episode type I bipolar patients 18–72 years | 4.7 years | Mania: major episode or sub-syndromal | Every 3 months | DSM-IV/ LIFE | Exceeding sporadic usage according to patient | 30 (18.1%) | Cannabis use during preceding quarter significantly associated with mania (11.1% excess risk) | Age, sex, years of total exposure time | Inclusion of hypomania (i.e., sub-threshold mania) may have reduced accuracy |
| Duffy et al. (2012) | High-risk cohort | 211 high-risk adolescents 12+years | 5.2 years (mean) | Bipolar disorder 35 (16.6%) | Baseline and annually | DSM-IV/ KSADS-PL | DSM-IV criteria for substance use disorder (SUD) | 35 (16.58%) | A priori SUD significantly predicted development of bipolar disorder (Hazard Ratio: 3.40) | Sex, socioeconomic status and familial correlation | Associations with SUD no cannabis use specifically |
| Henquet et al. (2006) | Prospective population study | 4815 individuals 18–64 years | 3 years | hypo/sub-threshold mania symptoms (1 ≥ mania item)<br>Rate of mania: Baseline: 192 (4%)<br>Follow-up: 118 (25%) | Baseline, 1 year, 3 years | CIDI | Lifetime and follow-up cannabis use<br>– any<br>– frequency | Baseline: 9.4% during follow-up: 3.9% | Baseline cannabis significantly predicted hypo/sub-threshold mania symptoms during follow-up (Odds Ratio: 2.51; 95% CI =1.38–4.59) | Age, sex, education, ethnicity, marital status, other drugs, neuroticism, alcohol, baseline depression, mania and psychotic symptoms | Sub-threshold definition of manic-like symptoms applicability to clinical levels unclear |
| Strakowski et al. (2000) | Prospective follow-up, 1996 | 50 bipolar patients aged 16–45 years | Max 2 years | Full or significant symptoms<br>Mania syndrome: -10% of time with mania | Every month, then every 4 months | YMRS | SCID-P<br>Full or significant | Exhibited cannabis abuse: 13% of time | Fraction of time with cannabis use associated with fraction of time with mania (Regression co-efficient: 0.42) | Age, gender, race, education, employment, affective state, age of bipolar disorder onset, duration of index episode, treatment noncompliance | Preliminary results as very small sample |
| Tijssen et al. (2010) | Prospective cohort community study, 1994 | 705 adolescents and young adults | 8 years | Mania (hypomania) symptoms (11 item scale)<br>Experienced manic symptoms: – follow-up: 79 (11.2%)<br>Baseline and follow-up: 46 (6.5%) | 1.6, 3.4 and 8.3 years | DIA-X/M-CIDI | Lifetime cannabis: used 5 times or more | 4.4% | Baseline cannabis significantly predicted (hypo) mania symptoms during follow-up (Odds Ratio: 4.26; 95% CI 1.42–12.76) | Age, sex, socioeconomic status, family history of mood episodes, exposure to trauma, loss of a parent, alcohol use, personality style | Sub-threshold outcome thus applicability to clinical levels unclear<br>Those with baseline mania (or hypomania) excluded reducing power |
| Van Rossum et al. (2009) | Prospective follow-up | 3426 bipolar in- and out-patients<br>Mean age 44.6 years | 1 year | Mania symptoms on a 7-point index<br>Mania mean (SD)<br>Baseline: 4.8 (1.0)<br>3 months: 2.2 (1.2)<br>6 months: 1.9 (1.2) | Baseline, 12 weeks, 6 months, 1 year | CGI-BP mania | Abuse or dependence | 436 (12.7%) | There was a significant association between any cannabis use and mania score during follow-up $B=0.15$, CI: 0.06, 0.24; $p=0.001$. | Country, sex, compliance, age of onset, use of alcohol and other drugs | Clinical sample with baseline rating of mania thus could only infer about the severity and persistence of symptoms (no causality) |

**Table 2**
Quality assessment of the included studies based on risk of bias.

| Study | Selection bias – random sequence generation | Selection bias – allocation concealment | Performance bias – blinding of participants and personnel | Detection bias – blinding of outcome assessment (patient-reported outcomes) | Attrition bias – incomplete outcome data | Reporting bias – selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Baethge et al. (2008) | High | High | Low | Low | High | Low | Low |
| Tijssen et al. (2010) | High | High | Low | Low | High | Low | High |
| Van Rossum et al. (2009) | High | High | High | High | Low | Low | Low |
| Henquet et al. (2006) | High | High | High | High | High | Low | Low |
| Duffy et al. (2012) | High | High | Low | Low | High | Low | Low |
| Strakowski et al. (2000) | High | High | High | High | High | Low | Low |

Exclusion of participants with manic and depressive symptoms at baseline resulted in a loss of power, which could have led to an underestimation of associations ('other' bias). In van Rossum et al. (2009) there was high risk of bias in selection (random generation and allocation concealment), performance and detection domains. Baethge et al. (2008) was classified as high risk in the domains of selection (random generation and allocation concealment) and attrition bias. In Duffy et al. (2012) high risk of bias in selection (random generation and allocation concealment) and attrition domains was also found.

### 3.3. *Does cannabis use worsen mania symptoms in individuals with pre-existing bipolar disorder?*

Using a small clinical sample of 50 new-onset bipolar patients aged 16–45 years, Strakowski et al. (2000) considered the impact of cannabis use on the course of bipolar disorder over 2 years. At one month, then 4 monthly intervals mania symptoms (full syndrome or significant symptoms) were assessed using the Young Mania Rating Scale (YMRS), while cannabis use was assessed using the Structured Clinical Interview for DSM-IV-Patient version (SCID-P). For each assessment interval the investigators made week-by-week ratings of the severity of substance abuse and mania symptoms. From these assessments the percentage of weeks with full (i.e., full syndrome, severe) or significant (i.e., marked symptoms; partial remission) substance abuse and mania symptoms was calculated. Regression analysis revealed that the duration of time with active cannabis use syndrome/symptoms (i.e., as defined by the percentage of weeks with full or significant symptoms) was significantly associated with the duration of time with mania syndrome/symptoms ($R=0.42$, $p<01$).

In a larger clinical study, Baethge et al. (2008) prospectively followed-up (mean length 4.7 years) 166 first episode DSM-IV bipolar I patients with a median intake age of 28 (range 18–72) years to assess the association between cannabis use (exceeding sporadic) and mania (major episode or hypomania according to DSM-IV). Using generalised estimating equation regression modelling the authors found that by quarters (i.e., 3 month periods) cannabis use strongly and selectively predicted (RC=0.111; 95% CI=0.054–0.168; $z$-score=3.80; $p<0.001$) manic symptoms or episodes. Conversely, substance use was not preceded by mood states in the previous quarter. Associations with manic symptoms were reported to be specific. Cannabis use did not predict depression symptoms and alcohol use did not predict mania symptoms. While the authors concluded that these findings suggest potential 'causal' associations between cannabis use and mania, it should be borne in mind that cannabis use also coincided with manic symptoms during the same quarter (RC=0.116; 95% CI=0.053–0.178; $z$-score=3.63; $p<0.001$), indicating the possibility of reverse causality (i.e., cannabis use could have occurred in the context of existing mania symptoms).

van Rossum et al. (2009) explored the association between cannabis use and mania symptoms over the course of a year in a very large sample ($N=3426$) of bipolar in-and out-patients. Mania symptoms were assessed using the Clinical Global Impression Bipolar (CGB-BP) mania scale and rated for severity on a seven point index (yielding a total mania symptom score) at baseline, 12 weeks, 6 months and 1 year. Cannabis use was dichotomised into 'any cannabis use,' incorporating any instances of use, abuse or dependence, versus 'no use.' As each assessment pertained to the preceding 3 months, any cannabis use referred to reported use at least once over the 15 month period. After controlling for baseline mania symptoms, sex, treatment compliance, age, age of onset (i.e., first symptoms of bipolar disorder) and use of alcohol and other drugs, multi-level random regression analyses revealed that any cannabis use was significantly associated with CGI-BP mania score ($B=0.15$, CI: 0.06, 0.24; $p<0.001$). The authors assessed 'any cannabis use' regardless of level of dependency or duration of use. Therefore, reported associations likely lacked precision, due to heterogeneity between individuals in terms of dependency, volume, frequency and duration of cannabis use. As has been observed for the course of psychosis (Moore et al., 2007), it is likely that the effects of chronic cannabis use on mania may be markedly different from those of short-term or occasional use.

### 3.4. *Does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?*

Tijssen et al. (2010) conducted an 8 year prospective, community study of 705 youth aged 14–24 years. Participants completed baseline, and three follow-up assessments. Lifetime cannabis use was defined as having used cannabis five or more times. Hypo (manic) symptoms were assessed using mania section of the Composite International Diagnostic Interview (CIDI). Items were rated as absent or present, thus a sum score of 0–11 was possible (dichotomised into 0–3=no mania symptoms; >3=mania symptoms). The association between cannabis use and onset of manic symptoms was calculated as the strength of association between

cannabis use at baseline and follow-up manic symptoms in the absence of manic symptoms at baseline. Onset of (hypo) manic symptoms was significantly associated with cannabis use, i.e., those reporting past cannabis use were approximately four times more likely to develop mania symptoms (OR: 4.26; 95% CI 1.42, 12.76; $P < 0.01$).

In a larger general population study of 4185 individuals aged 18–64 years Henquet et al. (2006) explored the prospective association between cannabis use and sub-threshold mania symptoms. Cannabis use (any and frequency) and manic symptoms were assessed using the CIDI. In unadjusted analysis, cannabis use was associated with a 5 times increased risk of mania symptoms (i.e., at least one positive rating on any of the 11 items of the CIDI) at follow-up. While attenuated following control for sociodemographic variables, neuroticism, use of other drugs and alcohol, baseline mania and psychosis symptoms, the association between cannabis use and mania remained significant. Furthermore, a dose response association was observed. The strength of association between cannabis use and mania symptoms was nearly double for cannabis use on 3–4 days per week (OR: 6.94; 95% CI: 2.00–24.06) in comparison to 1–2 days per week (OR: 3.78; 95% CI: 1.59, 8.97).

In a recent study, Duffy et al. (2012) used a high-risk offspring cohort of 211 adolescents aged 12 years and older to assess the association between lifetime substance use disorder (SUD) and bipolar disorder (NOS, BDI, and BDII). All offspring were assessed annually using the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL) interview. Lifetime substance use disorder (23.7%) was classified according to DSM-IV criteria, with cannabis use being the most common disorder (70% of SUDs). Bipolar disorder showed a bidirectional relationship with SUD. Cox Proportional Hazards (CPH) analysis revealed that having an a priori SUD predicted the subsequent development of bipolar disorder (Hazard Ratio: 3.403; $p < 0.01$). Conversely, bipolar disorder increased the risk of subsequent substance use disorder (Hazard Ratio: 3.066; $p < 0.01$). When appraising these results it should be noted that while cannabis use was the first drug of abuse in 70% of the SUD cases, some individuals reported alcohol abuse disorder with subsequent cannabis use, and a very small proportion reported poly substance abuse. This heterogeneity could have confounded the reported associations between cannabis use and bipolar disorder, though studies have indicated that alcohol abuse may be associated with depression rather than mania symptoms in bipolar disorder (Baethge et al. 2008; Strakowski et al., 2005).

### 3.5. Meta-analysis results

Two community studies (Henquet et al., 2006; Tijssen et al., 2010) provided information suitable for synthesis using meta-analytical techniques (i.e., they provided a cannabis-mania association value which could be meaningfully pooled and converted into a common effect size (Field and Gillett, 2010)). There was a low, non-significant degree of heterogeneity between studies ($I^2 = 0.00$; $p = 0.469$). The pooled effect size (displayed in Fig. 2) for the association between cannabis use and mania symptoms was: Odds Ratio = 2.97 (95% Confidence Intervals: 1.80, 4.90).

## 4. Discussion

We completed a comprehensive systematic review of the extant literature in an attempt to establish whether cannabis use may worsen mania symptoms in those formerly diagnosed with bipolar disorder, and also trigger onset of manic symptoms in those without prior diagnosis. Specifically, we were interested in the independent associations between cannabis use and subsequent mania as distinct from psychotic symptoms. Collectively, the findings from the systematic review and meta-analysis suggest that there is a significant relationship between cannabis use and subsequent exacerbation and onset of mania symptoms. Results from the meta-analysis demonstrated that cannabis use was associated with an almost three-fold increase in the odds of mania symptoms in non-clinical populations, indicating a moderate association (Ferguson, 2009).

### 4.1. Does cannabis use increase the occurrence of manic symptoms or mania in those with pre-existing bipolar disorder?

Collating results from studies utilising clinical populations, it can be concluded that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases (van Rossum et al., 2009; Strakowski et al., 2000; Baethge et al., 2008). Previously, it has been unclear whether cannabis use predates manic episodes represents a symptom of bipolar disorder or an attempt to self-medicate, or that both disorders share common risk factors (Strakowski and Delbello, 2000). Evidence here mainly supports the contention that cannabis use precedes the presence/re-occurrence of manic symptoms in at least a proportion of the population previously diagnosed with bipolar disorder. For example,

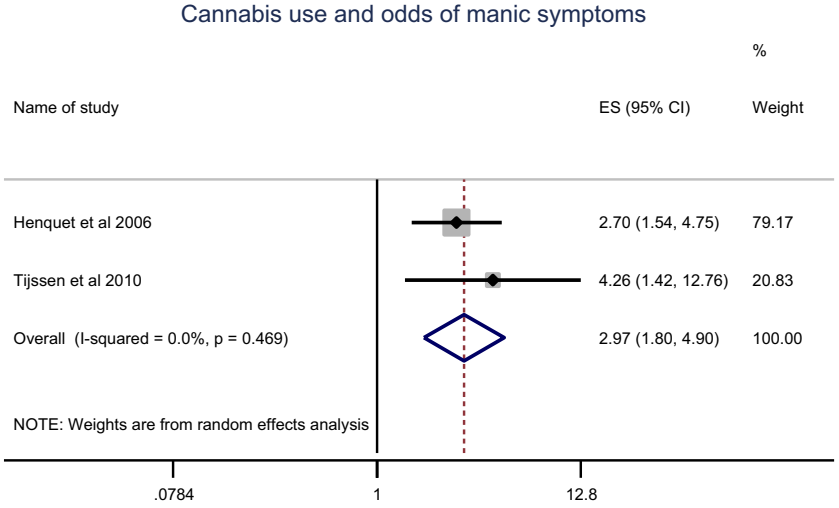


**Fig. 2.** Cannabis and manic symptoms.

Baethge et al. (2008) reported that while cannabis use preceded mania symptoms, there was no reciprocal pattern, i.e., mania did not precede cannabis use. Further, van Rossum et al. (2009) reported an association between cannabis use and mania after controlling for baseline mania symptoms, supporting that cannabis use is associated with new manic symptoms. While these findings are suggestive, it should be acknowledged that both Baethge and van Rossum studied patients with an existing diagnosis of bipolar disorder; thus it is possible that low level (i.e., below the study threshold) mania symptoms can have exacerbated the likelihood of subsequent cannabis use. The clinical studies reviewed here also indicate a degree of *specificity* regarding the associations between cannabis use and mania symptoms in bipolar populations. In two studies, the duration of cannabis abuse was significantly associated with the duration of mania (Strakowski et al., 2000; van Rossum et al., 2009). Furthermore, while cannabis use appears to selectively precede mania symptoms, it has not been found to be similarly associated with depression symptoms (Baethge et al., 2008).

### 4.2. Does cannabis use induce mania symptoms specifically?

While results from clinical populations can inform us regarding the course and severity of bipolar disorder as a result of cannabis use, non-clinical population studies (which assess cannabis use *prior* to the *onset* of the disorder) are required in order to understand whether a consistent and strong signal emerges with regards to possible causality. High-risk offspring population studies and community cohorts of adolescents and young people prospectively followed over time suggest that cannabis use is associated with bipolar disorder (i.e., NOS, BDI, and BDII) (Duffy et al., 2012) and mania symptoms (Henquet et al., 2006). Importantly, Henquet et al. (2006) found that baseline cannabis use predicted sub-threshold mania symptoms during follow-up once baseline mania symptoms and a number of important confounders such as psychotic symptoms were statistically accounted for, supporting that cannabis use may contribute to the development of non-psychotic mania symptoms specifically (Van Laar et al., 2007). While population studies are suggestive of a causal association between cannabis use and the onset of mania, it should be borne in mind that mania symptoms are considered in terms of sub-threshold levels in these studies (Henquet et al., 2006; Tijssen et al., 2010). Thus, the clinical relevance of these findings remains uncertain. Nevertheless, as has been described for sub-threshold psychosis symptoms (Van Os et al., 2009), research suggests that expressions of mania outside the realm of clinical disorder have a distribution in the general population (Akiskal, 2003; Krabbendam et al., 2004) and that sub-threshold expressions of mania show continuity with clinical diagnoses of mania and thus bipolar disorder (Regeer et al., 2006; Thomas, 2004).

### 4.3. Potential mechanisms underlying the association between cannabis use and manic symptoms

Pharmacological and brain imaging studies suggest that dopaminergic hyperactivity may underlie both psychosis and mania. Both disorders share a genetic predisposition towards dysregulation of the dopamine system, which may be exacerbated by social or pharmacological stress (Murray et al., 2004). An increase in positive psychotic symptoms in response to cannabis use has been linked to its main psychoactive component tetrahydrocannabinol (THC), which appears to enhance mesolimbic dopaminergic activity (D'souza et al., 2005). In addition, cannabinoid receptors, such as CB1, appear to decrease the uptake of dopamine, potentiating its actions (D'souza et al., 2005). Therefore, as has been described for schizophrenia, cannabis use may contribute to the development of mania symptoms by leading to a sensitisation of the dopaminergic system (Sarkar et al., 2003). 'Sensitisation' in this case refers to a process by which intermittent cannabis exposure produces a permanent change in dopaminergic responses (Wolf et al., 1993). Thus, regular cannabis use may render individuals gradually more sensitive to dopamine- induced perceptual and cognitive abnormalities (De Hert et al., 2011), Indeed, Henquet et al. (2006) reported that while baseline cannabis use was significantly associated with mania symptoms at follow-up, a similar association between *follow-up* cannabis use and mania was not observed. This supports that the effects of cannabis use on manic symptoms may result from long term rather than acute exposure.

### 4.4. Limitations

Although we were comprehensive in the data sources reviewed, we were able to identify only a relatively small number of studies on which to base our conclusions. The scarcity of available studies, and variations in assessment tools and statistical approaches, limited our ability to present a full quantitative synthesis of the data (e.g., meta-regression techniques to explore associations independent of confounding study factors). Furthermore, all studies demonstrated risk of bias in at least 3 (and usually more) out of 7 domains, and our findings should also be seen in this light.

Studies were variable in terms of the precision of assessment of cannabis use. For example, some studies indicated cannabis use according to 'any cannabis use,' regardless of severity or frequency of use (van Rossum et al., 2009; Baethge et al., 2008). Duffy et al. (2012) did not differentiate cannabis users from other substance users, though the majority of participants primarily used cannabis. There were also wide variations in the assessment of mania symptoms. Duffy et al. (2012) considered associations with bipolar disorder (BPI, BPII, and NOS) rather than mania symptoms per se. While BPI diagnosis necessitates only a single manic episode, BPII requires both hypomanic and depressive episodes (APA, 2000). Therefore, associations in this study may have lacked specificity. Other studies conflated sub-clinical with clinical levels of mania (Strakowski et al., 2000) or used a low threshold for the presence of mania symptoms (Henquet et al., 2006).

To establish whether cannabis use triggers manic affective symptoms specifically, we sought to exclude all studies which included patients with a psychotic disorder. In some of the included studies, however, participants were experiencing a degree of psychotic symptoms (van Rossum et al., 2009; Duffy et al., 2012; Henquet et al., 2006), which were significantly associated with cannabis use. Unfortunately, only one of these studies, as far as we can discern, simultaneously controlled for psychotic symptoms when assessing the association between cannabis use and mania symptoms (Henquet et al., 2006). Other studies did not assess psychotic symptoms (Baethge et al. 2008; Strakowski et al. 2000; Tijssen et al. 2010), precluding assessment of mania–cannabis associations while concurrently adjusting for psychotic symptoms. In the absence of further studies in this vein, the observation of an independent (of psychosis symptoms) association between cannabis use and mania remains tentative.

Our inclusion of prospective studies only, while necessary to tease out the directionality of effect, also reduced the number of available studies, highlighting the need for more well-designed epidemiologic prospective studies in order to trace the pathways from cannabis use to mania symptoms (Castle and Murray, 2004). Also even in our selection of prospective studies, it was not always clear that manic symptoms were being assessed in the absence of continued cannabis use (Strakowski et al. 2000; Baethge et al. 2008) raising the possibility that at least some manic symptomatology could be explained by intoxication effects or reverse causality. Finally, due to the observational nature of the identified review papers, we remain tentative in our conclusions regarding the *causal* link between

cannabis use and mania symptoms. While cannabis use appears to predate mania, it is always possible that the observed associations may be attributable to unidentified third variables (Castle and Murray, 2004). Insomnia (Bauer et al., 2006; Leibenluft et al., 1996; Colombo et al., 1999; Ashton et al., 2005) and childhood maltreatment (Bender and Alloy, 2011; Thornberry et al., 2010), for example, have both been associated with cannabis use and mania; however, these factors were not included as confounders in the reviewed articles.

### 4.5. Implications for clinical and research practice

In sum, the observed tendency for cannabis use to precede or coincide with rather than follow mania symptoms, and the more specific association between cannabis use and new onset manic symptoms, suggests potential causal influences from cannabis use to the development of mania (Baethge et al., 2008). The symptom overlap between mania and psychosis suggests that the reasons postulated to explain the cannabis-psychosis link may also be part of the explanation of the cannabis-mania association, though of course other mechanisms may exist. It is also important, however, for future studies to consider specific pathways from cannabis use to mania and how these may be modulated by genetic vulnerability and environmental risk factors (Murray et al., 2004).

Bipolar patients with co-morbid substance abuse have more severe symptoms and an increased risk of relapse, though the extent to which severe symptoms are predictive, or a consequence, of increased cannabis use remains unclear. Regardless, such patients merit special clinical consideration (Richardson, 2013). Cannabis is the most prevalent drug used by the under-18s (National Treatment Agency, 2012) and during this critical period of development (Paus et al., 2008) services should be especially aware of and responsive to the problems that cannabis use can cause for adolescent populations (NTA, 2012).

It has been established that there are limited studies addressing the association of cannabis use and manic symptoms, which suggests that this is a relatively neglected clinical issue, possibly due to the methodological and practical difficulties inherent in bipolar disorder research (Murphy and Sahakian, 2001). However the reviewed evidence supports that cannabis use is a major clinical problem occurring early in the evolving course of bipolar disorder (Tijssen et al., 2010) highlighting the importance of substance abuse prevention programs for youth (Paglia and Room, 1999) and developing and utilising interventions for those with this type of dual diagnosis.

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# 12
# Mental Health

| Chapter Highlights |
| --- |
| • Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk.<br>• In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.<br>• Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.<br>• For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.<br>• Heavy cannabis users are more likely to report thoughts of suicide than non-users.<br>• Regular cannabis use is likely to increase the risk for developing social anxiety disorder. |

The relationship between substance use and mental health has been a long-standing and complex public health issue. In 2014, a national survey from the Substance Abuse and Mental Health Services Administration found that 20.2 million adults had a substance use disorder, and of these individuals, 7.9 million had both a mental health disorder and a substance use disorder (SAMSHA, 2015). These statistics emphasize the importance of conducting cross-disciplinary research in order to appropriately inform public health decisions and ultimately improve population health. In this chapter, the committee reviews the current evidence on the association between cannabis use and prioritized mental health outcomes.

The mental health outcomes selected for review in this report were derived from the committee's statement of task and the sponsors' expressed interest, and based on committee consensus. Specifically, mental health outcomes with high prevalence (e.g., depression and anxiety disorders) were included, as were outcomes with significant public health implications such as suicide. Studies on the association between cannabis use and schizophrenia and psychosis were included based on the large volume of literature on the subject, and in an effort to evaluate cannabis effects across mental health diagnostic spectrum, studies on the association between cannabis use and bipolar disorder were reviewed as well.

Concerning each disorder, the committee focused on two key questions: What is the effect of cannabis use on the risk of developing the disorder? And in patients with the disorder, what are the effects of cannabis use on the symptoms or course of the disorder? An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles (e.g., cross-sectional studies, case-control studies, cohort studies, randomized controlled trials [RCTs], or non-systematic literature reviews) for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies that would likely produce the clearest research conclusions. For example, for the health endpoints discussed below, literature searches were limited to articles that included the following

search terms: longitudinal, prospective, and case-control.[1] The committee's review of the literature focused on identifying studies relevant to answering these specific questions. In this chapter the committee will discuss the findings from 14 of the most recent, good- to fair-quality systematic reviews and from 31 primary literature articles that best address the committee's research questions of interest.

It is important to note that the present review does not include findings from controlled laboratory studies. These studies have been used to assess the effect of cannabis on behavior, to understand how cannabis interacts with alcohol and other drugs to influence behavior, and to characterize the dose-dependent effects of cannabis as they relate to its potential for addiction. Evidence from this body of research—though illuminating at the mechanistic level—does not provide information on the mental health effects of cannabis use in real-world conditions, and was excluded for this reason.

**BOX 12-1**
**Co-Morbidity in Substance Abuse and Mental Illness**

National survey studies suggest that it is not uncommon for individuals with mental health disorders to use substances of abuse and, likewise, that it is not uncommon for individuals who abuse or are dependent on drug substances to also meet diagnostic criteria for a mental health disorder. In fact, in a 2014 national survey, almost 8 million adults in the United States reported co-occurring substance abuse and mental health disorders. This co-occurrence is also termed, *co-morbidity*.

There are a number of proposed explanations for why the co-morbidity of substance abuse and mental health disorders exists. Three of the most commonly explored hypotheses are:

1. *Substance use may be a potential risk factor for developing mental health disorders.* Given the overlap in associated neurochemical substrates (e.g., dopamine, serotonin), specific neurobiological alterations due to drug use, may have resulting effects on the neural processes regulating mental health.
2. *Mental illness may be a potential risk factor for developing a substance abuse disorder.* Research suggests that individuals who are at risk for a mental health disorder, or those who experience subclinical symptoms, may be more likely than others to use drugs as a form of self-medication.
3. *An overlap in predisposing risk factors (e.g., genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder.* Studies suggest that the development of mental health disorders and substance abuse disorders may be a symptomatic outcome of pre-existing neurobiological abnormalities (e.g., receptor abnormalities, epigenetic modifications).

Although the precise explanation is still unclear, it is reasonable to assume that co-morbidity between substance abuse and mental health disorders may occur due to a mixture of proposed scenarios. With this context in mind, however, it is important to note that the issue of co-morbidity directly affects the ability to determine causality and/or directionality in associations between substance use and mental health outcomes. This is a complex issue, one that certainly warrants further investigation.

SOURCES: Center for Behavioral Health Statistics and Quality, 2015; EMCDDA, 2016; NIDA, 2011.

[1] The initial search of the primary literature produced a relatively small literature base for the posttraumatic stress disorder section, and as such, the additional search restrictions were not applied.

## SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints. Therefore, conclusions regarding the association between cannabis use and psychosis are in general not diagnosis specific.

### Is There an Association Between Cannabis Use and the Development of Schizophrenia or Other Psychoses?

*Systematic Reviews*

Five systematic reviews of fair or higher quality were identified that addressed the committee's research question (Large et al., 2011, Marconi et al., 2016, Moore et al., 2007, Myles et al., 2012, van der Meer et al., 2012). While the systematic review by Marconi et al was the most recent, it excluded studies that did not consider at least three levels of cannabis exposure because the researchers' main purpose was to address dose–response relationships. In addition to reporting on the systematic review by Marconi et al., the systematic review conducted by Moore et al is also discussed.This study addressed the broad question of cannabis use and psychotic outcome and included meta-analysis results. The remaining systematic reviews, which are not reported on here, focused on the time to onset of psychosis (or the age of onset of psychosis), the role of concomitant tobacco use, and psychotic symptomatology in patients at high risk of psychosis.

The systematic review by Marconi et al. (2016) included a search of the literature through December 31, 2013, and selected 10 studies for inclusion in the meta-analysis. A key feature of the researchers' inclusion criteria was the requirement that studies assess cannabis use with a dose criterion and classify cannabis use into at least three exposure groups. Thus, high-quality studies with cannabis assessed as a dichotomous variable were excluded from the analysis. Studies that reported psychotic symptoms on a continuous, rather than categorical, scale were also excluded from the analysis. The 10 studies reviewed were conducted in Australia, Europe, New Zealand, and the United States and reported results for 66,816 individuals. The age and sex of the subjects were not reported. Cannabis use was classified based on lifetime frequency, the frequency of use at baseline, the duration/frequency of current use, and frequency within the last year. The authors did not assess the quality of the papers included in the meta-analysis, but they did conduct analyses to assess publication bias and heterogeneity. They considered the publication bias to be low and acknowledged the existence of heterogeneity within their sample of studies. Marconi et al., (2016) found an association between cannabis use and psychosis (odds ratio [OR], 3.9; 95% confidence interval [CI] = 2.84–5.34) among the most severe cannabis users, as compared to the nonusers. The investigators also report a dose-response relationship with an OR of 1.97 (95% CI = 1.68–2.31) for those at the median of any cannabis use and an OR

of 3.40 (95% CI = 2.55–4.54) for those in the top 20 percent of cannabis use. In addition, they reported associations of cannabis use with the presence of psychotic symptoms (pooled odds ratio [pOR], 3.59: 95% CI = 2.42–5.32), as well as with a diagnosis of schizophrenia or psychotic disorder (pOR,5.07; 95% CI = 3.62–7.09). Subgroup analysis stratified by study design revealed a pooled odds ratio of 3.99 (95% CI = 2.50–6.37) for cross-sectional studies and 3.83 (95% CI = 2.34–6.29) for cohort studies.

Moore et al. (2007) searched multiple databases from their inception through September 2006 and included only studies that were longitudinal, population-based, or case-control studies nested within longitudinal designs. They assessed study quality by recording information on sampling strategy, response rates, missing data, attrition, attempts to address reverse causation, intoxication effects, and other potential confounders. Their search identified 32 studies, with 11 studies reporting the incidence of psychosis from 7 cohort studies, 5 of which were adult population-based cohorts and 2 of which were birth cohorts. They found no evidence of the presence of publication bias using Egger's test (p = 0.48). The authors noted that some individual studies adjusted for psychotic symptoms at previous assessments or baseline and excluded people with psychotic symptoms or diagnosis at baseline to help clarify the temporal order of events. The authors also noted that individual studies excluded psychotic symptoms that arose solely from drug use by using scales to measure drug intoxication. In addition, this group of studies collectively adjusted for approximately 60 different potential confounders, including other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. In a pooled analysis, the authors found that in individuals that have ever used cannabis, there was an associated increased risk of a psychotic outcome (adjusted odds ratio [aOR], 1.41; 95% CI = 1.20–1.65). When the analysis was restricted to studies examining the effects of frequent cannabis use, the investigators found a stronger association (aOR, 2.09; 95% CI = 1.54–2.84), suggesting a dose–response relationship between cannabis use and the risk of a psychotic outcome.

*Primary Literature*

Auther et al. (2015) used the North American Prodrome Longitudinal Study[2] phase 1 sample to examine the impact of the level of cannabis use on conversion to psychosis.[3] From the subjects that contributed to the data, 370 were determined to be at a high risk for developing a psychotic disorder. After excluding subjects that were missing necessary outcome data, or who met criteria for attenuated positive symptom syndrome, brief intermittent psychotic syndrome, genetic high-risk, and deterioration syndrome, a total of 283 subjects (mean age = 18.3 years) were included in the study's analysis. Using the subjects' reported level of lifetime use, subjects were divided into three subgroups: no use, use without impairment, and abuse and dependence. The primary outcome, conversion to psychosis, was determined by meeting the full criteria for Presence of Psychotic Syndrome on the Structured Interview for Prodromal Syndrome.In a follow-up assessment (approximately 17 months after the initial baseline assessment), the researchers found that cannabis abuse/dependence was associated with a greater risk of

[2] The North American Prodrome Longitudinal Study is a collaborative database formed in 2007. The database contains data on various clinical, cognitive, and functioning variables collected from eight independent research centers.

[3] Auther et al. defined this outcome as having a psychotic level positive symptom that is either seriously disorganizing or dangerous, or that occurs for at least 1 hour per day for an average of 4 days in the past month.

conversion to psychosis within the chronic high-risk population; however, when alcohol use was incorporated into the Cox regression model, cannabis abuse/dependence was no longer significantly related to conversion (hazards ratio [HR], 1.875; 95% CI = 0.963–3.651). Similar research conclusions were reached in a longitudinal study by Valmaggia et al. (2014), where they examined the assocation between lifetime cannabis use, and the development of psychosis. Valmaggia et al. (2014) followed 182 individuals at ultra-high risk for psychosis disorder for two years and found that varying degrees of cannabis use (i.e., lifetime use, frequent use, early-onset use, and continued use after presentation) among lifetime cannabis users is associated with an increased transition to psychosis. It is of note, however, that within this specific ultra-high risk population, cannabis users were no more likely to develop psychosis than those who had never tried cannabis.

Using a case-control design of 410 patients with first episode psychosis and 370 population controls, Di Forti et al. (2015) showed that first-episode psychosis patients were more likely to have lifetime cannabis use, more likely to use cannabis every day, and to mostly use high potency cannabis, as compared to the controls. The cases were also more likely to have used cannabis before the age of 15. Duration of use did not differ between patients and controls, nor did other drug use. After adjusting for a variety of confounders including use of other drugs and alcohol, the researchers found an increased risk of developing psychosis in subjects who used cannabis daily (OR, 3.04; 95% CI= 1.91–7.76), and in subjects who used high potency cannabis (OR, 2.91; 95% CI = 1.52–3.60). In a cross-sectional study of subjects with first-episode psychosis, Colizzi et al. (2015) examined the association between cannabis use, the risk of psychosis, and the dopamine receptor type 2 polymorphism, rs1076560. Researchers found, after adjusting for confounders (e.g., gender, age, ethnicity, polysubstance use), a significant interaction between lifetime frequency of cannabis use and dopamine receptor type 2 (DRD2) polymorphism rs1076560 on psychosis risk. Moreover, a lifetime history of cannabis use was associated with an increased risk of having psychotic disorder in T carrying subjects, relative to GG carrying subjects (OR, 3.07; 95% CI = 1.22–7.63).[4]

*Discussion of Findings*

The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors. Factors contributing to the strength of the evidence derived from the cited systematic reviews include large sample sizes, the relative homogeneity of the findings, the presence of relationships between the dose/exposure and the risk, the studies having been controlled for co-founders, and the systematic reviews having assessed for publication bias. The primary literature reviewed by the committee confirms the conclusions of the systematic reviews, including the association between cannabis use and psychotic outcome and the dose-dependency of the effects, further bolstering the overall strength of evidence for our conclusions.

The limitations of the summarized studies include their reliance of self-report for cannabis use, issues with study designs (e.g., a lack of randomization), a lack of information on

[4] T carrying subjects have at least one allele with the polymorphism. G carrying subjects do not express the polymorphism. Genotype results of the subjects included: homozygote G/G, heterozygote G/T, and homozygote T/T genotype classes. Due to the low number of subjects with TT subjects, G/T and T/TT subjects were combined and compared to G/G carriers.

the frequency of use, patterns of long-term use, and possible confounding polysubstance effects. In addition, for the primary studies cited, some are also limited in terms of their sample sizes and controlling for confounders. Overall, the accumulated evidence is suggestive that cannabis use is associated with an increase in psychosis-related outcomes, as made evident in the discussion of Auther et al., 2015, and Valmaggia et al., 2014, above.

As noted in Box 12-1, the relationship between cannabis use, cannabis use disorder and psychoses may be multi-directional and complex. The committee found this to be consistent with their review of the summarized data demonstrating a strong and consistent association between cannabis use and the subsequent development of psychosis and psychotic disorders. In addition, it is noteworthy to state that in certain societies, the incidence of schizophrenia has remained stable over the past 50 years despite the introduction of cannabis into those settings (Kirkbride et al., 2012); however, the committee did not examine ecologic data (studies of concomitant time trends) to evaluate trends in cannabis consumption and diagnosis of psychosis over time. Multiple factors (including measurement of dose and frequency of cannabis consumption over decades, and patterns of diagnosis of psychosis) limit our ability to draw conclusions from such findings. Of note, future analysis of rates of psychosis in states with increased access to cannabis could be tracked to provide valuable information regarding potential causal relationships between cannabis use and psychosis.

**CONCLUSION 12-1** There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.

### Is There an Association Between Cannabis Use and the Course or Symptoms of Schizophrenia or Other Psychoses?

*Systematic Reviews*

**Positive Symptoms** One systematic review was identified assessing the effects of cannabis use on positive symptoms[5] in patients with psychotic disorders, but the researchers did not conduct a quantitative synthesis of the findings (Zammit et al, 2008). An additional systematic review (Szoke et al 2014) addressed the effects of cannabis on schizotypal symptom dimensions, however, the committee will only report on the conclusions reported by Zammit et al (2008) because it provides information about patients with psychotic disorders rather than schizotypy.

After their assessment of the literature, Zammit et al. (2008) found mixed evidence for the effects of cannabis use on positive symptoms in patients with psychotic disorders, with studies reporting statistically significant but small associations between cannabis use and the severity of positive symptoms. The authors searched multiple databases through November 2006, screened 15,303 references, and identified 13 cohort studies (n = 1,413) for their review. Studies were included if they were longitudinal or were case-control studies nested in longitudinal designs to assure that cannabis use was measured before outcome ascertainment. The authors excluded cohorts of individuals with dual diagnoses (psychosis and cannabis misuse or dependence) because of the limitations on comparisons to control groups. The authors assessed the quality of the studies by comparing the response rate at baseline, loss to follow-up,

[5] Positive symptoms of schizophrenia may include delusions, hallucinations, or abnormal motor behavior.

masking of outcome assessment, adjustment for baseline severity, adjustment for alcohol and other substances, and adjustment for confounders. Their quality assessment is reported in a summary table, and the authors noted that the most likely source of confounding would be the lack of adjustment for baseline severity and a lack of adjustment for alcohol and other substances in several of the studies. The authors did not report sample sizes, the age or sex of the study participants, or the definitions of cannabis use. The authors noted that several of the reviewed studies varied in their consideration of confounders, such as the use of other substances and baseline symptom severity, and that the lack of an association may be explained by a random misclassification of exposure data, particularly self-reports of cannabis use.

**Negative Symptoms** In the systematic review described above, Zammit et al. (2008) identified four studies (from the 13 cohort studies identified in the larger systematic review) that assessed the effects of cannabis use on negative symptoms[6] in patients with psychotic disorders. As described above, Zammit et al. (2008) did not conduct a quantitative analysis of findings, but in their review they found that cannabis use was not associated with negative symptom scores in three studies, but that it was associated with reduced negative symptoms scores in a fourth study. It should be noted that the fourth study did not control for confounders or baseline differences in symptoms.

**Cognition** Three systematic reviews were identified that assessed the relationship between cannabis abuse and dependence and cognition effects (e.g., disorganized thinking) in patients with psychotic disorders (Donoghue and Doody, 2012, Rabin et al 2011, Yucel et al., 2012). A distinctive feature of this group of studies is the varying approaches to separating cannabis use from other substances. While the systematic review by Donoghue and Doody reported on all types of illegal substance abuse, it identified a sub-group of three studies focusing on cannabis use. This is in contrast to the work of Yucel and colleagues who included studies with patient groups who abused substances other than cannabis, and by Rabin et al., who considered cannabis use without other substance use, but relied on cross-sectional studies only.

Donoghue and Doody (2012) conducted a search for relevant studies published between 1980 and October 2010, and from an initial pool of 7,075 studies, the authors selected 19 studies for further review. Three of the 19 studies focused on cannabis use. The three studies (n = 551) used the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria to define cannabis abuse or dependence, and DSM-IV criteria to define schizophrenia or schizoaffective disorders. All three studies included inpatients and outpatients, as well as patients with a dual diagnosis. In their review of these studies, the authors found that cannabis users performed better on various measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than non-cannabis users. The authors conducted a meta-analysis of the three studies and reported statistically significant associations between cannabis use and verbal learning and memory (Hedges g[7] = 0.351, 95% CI = 0.179–0.523), attention and psychomotor (Hedges g = 0.316, 95% CI = 0.144–0.488), and global cognitive factor (Hedges g = 0.237, 95% CI = 0.083–0.390). Tests of association with working memory and executive function were not statistically significant.

[6] Negative symptoms of schizophrenia may include diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia.

[7] Hedges g reports the unbiased estimate of the effect size (the standardized difference between two means). It is commonly used for small sample sizes.

Rabin et al. (2011) conducted a meta-analysis on 8 cross-sectional studies, published between 2005 and 2010, with a total of 942 patients with schizophrenia. The 356 cannabis users among those patients had a mean age of 28.7 years, 81.9 percent were male, and had a mean education of 11.4 years. 586 of the 942 patients were nonusers of cannabis and had a mean age of 32.4 years, 65.8 percent were male, and had a mean education of 12.2 years. Limited information was provided about the statistical analysis, and the authors reported moderate associations with cannabis users performing better on general cognitive ability and intelligence; selective, sustained and divided attention; and visual-spatial and constructional abilities.

Yucel et al. (2012) searched the literature for the period 1987–March 2010 and included studies where cannabis was the predominant substance used by patients. They identified 10 studies involving 572 patients with schizophrenia; the studies were stratified by lifetime versus current or recent use. From their review, Yucel et al. (2012) found that patients with established schizophrenia and a history of cannabis use showed better performance on tests assessing cognitive abilities than did patients who did not use cannabis. For example, the meta-analysis conducted on 10 studies to assess global cognition, resulted in a Cohen's d[8] of 0.35 (95% CI = 0.09–0.61; p = 0.009), showing small to moderate increases in performance in cannabis users compared to non-users. Other small to moderate statistically significant effects were observed, again showing better performance by cannabis users compared to non-users for processing speed, visual memory, and planning, despite the smaller number of studies available for these comparisons. The authors stated that tests for publication bias or heterogeneity were conducted, but these were only partially reported. No differences were reported for assessments of attention, verbal memory or working memory.

*Primary Literature*

**Positive Symptoms** In a 2004 case control study with schizophrenic patients, Rehman and Farooq (2007) determined that patients with cannabis abuse had higher rates of positive symptoms than non-users. Seddon et al. (2016), in a case control study examining cannabis use in the first year following a first-episode psychosis, found that cannabis use at baseline or the 1-year assessment was associated with greater severity of positive symptoms (as measured by the Positive and Negative Syndrome Scale [PANSS] 2.14; 95% CI = 1.41–2.88) and a decrease in global functioning (as measured by the Global Assessment of Functioning symptom scale (-3.27; 95% CI = -6.04 to -0.49)). In contrast, Barrowclough et al. (2013) found no association between cannabis use and positive symptoms in patients with non-affective psychotic disorders, as assessed by PANSS; adjusted coefficient = 0.07 95% CI = -0.21–0.34). Moreover, using a longitudinal analysis over 24 months, the researchers found that changes in cannabis dose did not predict changes in positive symptoms severity, even when patients became abstinent. In their study, the researchers conducted a cross sectional analysis of 160 patients with a clinical diagnosis of non-affective psychotic disorder and a DSM-IV diagnosis of drug and/or alcohol dependence or abuse. Notable strengths of this study are its dose-response analysis and its detailed quantification of cannabis use, with mean use in the sample being 4 days/week and average of 2.4 grams per day. However, the results were not adjusted for confounders, including other drug use.

Another study, Dubertret et al. (2006) conducted a cross-sectional analysis on 205 patients with schizophrenia (n = 121 with no substance abuse; n = 38 cannabis users) and found

[8] Cohen's d is an estimate of the effect size (the standardized difference between two means).

that after controlling for other substance use, no association between cannabis use and positive symptoms was evident. A cross sectional analysis by Tosato et al. (2013) (n = 311 patients), found no association between cannabis use and the severity of positive symptoms in a population of first-episode psychosis patients. Similarly, in a prospective, longitudinal, cross-sectional study by Barrowclough et al. (2015) found no specific association between cannabis dose and positive symptoms (n = 102; adjusted coefficient, 0.01; 95% CI = −0.24–0.25), and reductions in cannabis use during follow-up (longitudinal analysis up to 18 months) were not associated with improvements in positive PANSS symptoms in cannabis-using subjects after adjusting for confounders including other drug use (n = 65; adjusted coefficient, -0.12; 95% CI = −0.45–0.22). After adjustment for confounders, abstinence from cannabis (90 days preceding the assessment) was found to be related to improved global functioning (adjusted coefficient, 4.95; 95% CI = 0.46–9.44). After controlling for confounders, van Dijk et al. (2012) found no difference between cannabis users (n = 68) and non-users (n = 77) with schizophrenia with regard to the severity of baseline schizophrenia symptoms (p = 0.61; assessed by the Clinical Global Impression scale). The researchers also found no relationship between amount of cannabis used and the level of psychopathology (p = 0.676; as measured by PANSS).

**Negative Symptoms** Dubertret et al. (2006), using a cross-sectional analysis, found that after controlling for other drug substances, cannabis use was strongly associated with fewer negative symptoms of avolition—apathy (p = 0.0001), as compared to non-cannabis users. Barrowclough et al. (2013), also using a cross sectional analysis, found that previous 90-day cannabis use was not significantly associated with the severity of negative symptoms (adjusted coefficient, 0.12; 95% CI = -0.05–0.29). The longitudinal analysis of data from this cohort (up to 24 months) revealed no association between cannabis dose and negative symptom severity (adjusted coefficient, 0.18; 95% CI = -0.14–0.51). Similarly, a prospective longitudinal study by Barrowclough et al. (2015) found no association between cannabis dose and negative symptoms after adjustment for confounders including other drug use (adjusted coefficient, 0.28; 95% CI = -0.04–0.61. Seddon et al. (2016) found that cannabis use at baseline or the 1-year assessment was not associated with differences in negative symptoms relative to non-users (as measured by PANSS; -0.07; 95% CI = -1.11–0.97)).

**Cognition** Power et al. (2015) found no association between lifetime cannabis use or cannabis dependence and cognitive function after controlling for confounding variables including the onset of illness and co-morbid cognitive functioning in Australian patients with an established *International Classification of Diseases-10* (ICD-10) diagnosis of psychotic disorder. Sanchez-Torres et al. (2013) used a longitudinal study to examine the impact of lifetime and current cannabis use on cognition in 42 patients with schizophrenia and found a negative effect of longitudinal cannabis use specifically in the social cognition domain (Pearson correlation, -0.34; $p < 0.05$). Van Winkle et al. (2011) found that cannabis use before the onset of psychosis interacted significantly with the rs2494732 single nucleotide polymorphism of the AKT1 gene to affect patient reaction time and accuracy as measured by the Continuous Performance Test. Cannabis-using patients with the a priori vulnerability (i.e., homozygous for the polymorphism) were slower and less accurate on the CPT than non-users.

*Discussion of Findings*

With regard to the effects of cannabis use on positive symptoms the data are considered mixed. Studies report both worsening and no effect of cannabis use on positive symptoms in schizophrenia. The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity, issues with study design (observational), a reliance on self-reports, and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime). However, these studies combined with human experimental studies demonstrating that cannabis can worsen positive symptoms in patients with schizophrenia were also considered when determining the strength of evidence. With regard to negative symptoms, the data reviewed were generally more homogenous with most studies reporting either an absence of association between cannabis use and negative symptoms, or else reduced negative symptoms in cannabis users. Variable adjustments for other drug use and baseline symptom severity were noted as limitations in some studies. Overall, the data provide support for the conclusion that cannabis use does not worsen negative symptoms in patients with psychotic disorders. With regard to cognition in patients with psychotic disorders, the data reviewed in the systematic reviews suggest better cognitive performance in some cognitive domains in patients with psychotic disorders and cannabis use disorders, and in patients with a history of cannabis use, as compared to patients with psychotic disorders and no cannabis use disorder diagnosis. The limitations of two of the systematic reviews, Yucel et al. (2012) and Rabin et al. (2011), include their study design (cross-sectional only), variable adjustments made for confounders, including other drug use, and variable definitions and inclusion criteria for cannabis using and non-using control groups. This study found better cognitive performance only in subjects with a lifetime history of cannabis use, but not recent cannabis use. The systematic review by Donoghue and Doody (2012) focused on longitudinal studies in schizophrenic subjects with and without co-morbid cannabis use and found that cannabis users performed better on some measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than non-cannabis users. The three reviewed studies showed similar effects; however, the largest study was more precise and had narrower confidence intervals. Estimates for the size of the effect are small to moderate. The primary articles reviewed indicate more mixed results than the systematic reviews.

Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of learning, memory, and attention (see Chapter 11). Among the multiple potential explanations of the data indicating better performance on certain measures of cognition in patients using cannabis, is that these patients represent a higher-functioning subgroup of psychotic patients, or that cannabis users who achieve abstinence have better premorbid cognitive status. Additionally, it has been proposed that a history of cannabis use may have exerted neuroprotective effects in patients with psychotic disorders. Finally, we find insufficient data from which to draw conclusions regarding the effects of cannabis on risk for suicide in patients with psychotic disorders.

**CONCLUSION 12-2**

**12-2(a)** There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance.

**12-2(b)** There is limited evidence of a statistical association between cannabis use and an increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders.

**12-2(c)** There is moderate evidence for no statistical association between cannabis use and worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders.

## BIPOLAR DISORDER

Bipolar and related disorders are categorized by episodes and/or symptoms of mania, hypomania, and depression (APA, 2013). The risk factors for developing bipolar disorder are not clear; however, research suggests that brain structure, genetics, and family history may contribute to its onset (NIMH, 2016). Given that cannabis is reportedly the most commonly used illicit drug by individuals with bipolar disorders (Zorrilla et al., 2014), it is worthwhile for this report to explore the potential association between cannabis use and the development and course of bipolar disorder.

### Is There an Association Between Cannabis Use and the Development of Bipolar Disorder or Mania?

*Systematic Reviews*

The committee identified one systematic review, Gibbs et al., 2015, that assessed the association between cannabis use and bipolar disorder or mania. The authors searched multiple databases for English language studies published through 2014 and included studies that were experimental, prospective, cohort or longitudinal. The overall search strategy yielded six studies with a total of 14,918 participants that met the inclusion criteria.Two of these studies, published in 2006 (n = 4815) and 2010 (n = 705) were used in the analysis. The meta-analysis showed an association between cannabis use and new onset of manic symptoms in individuals without pre-existing bipolar disorder (OR, 2.97; 95% CI = 1.80–4.90). However, the researchers did not report information about the patient characteristics, the total number of subjects, age, gender, cannabis form, the ascertainment of mania symptoms, or other features of the two studies. Furthermore, due to the low number of studies that contributed to their research findings, the authors describe their conclusions as prelimnary and tentative.

*Primary Literature*

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)[9] (Feingold et al., 2014) found that that any past-year use of cannabis was associated with the onset of bipolar disorder (OR, 2.24; 95% CI = 1.44–3.51) in unadjusted analyses. However, after adjusting for sociodemographic and clinical variables, the association was attenuated and no longer statistically significant (aOR, 1.17; 95% CI = 0.65–2.11).

Using the same NESARC dataset as Feingold, Cougle and colleagues (2015)[10] found that the risk of a past-year bipolar disorder diagnosis was elevated in regular (e.g., weekly use) cannabis users at Wave 2 follow-up: (OR, 1.37; 95% CI = 1.11–1.69). Cougle and collaborators reminded readers about the correlational nature of the study design and noted that causality could not be inferred from their conclusions. They also cautioned that the increased risk in bipolar disorders might be due to augmenting the psychotic features in frequent cannabis users (i.e., manic symptoms) that need further investigation. Also, Cougle and collaborators warned that in adjusting for other psychiatric comorbidities, they only adjusted for those that fulfilled diagnostic thresholds, but not other psychiatric symptoms that could explain the relationships of interest.

*Discussion of Findings*

Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine. For example, panel studies that have evaluated the relationship found the magnitude of the relationship to be similar, but once alcohol or other substances were adjusted for in the statistical models, the associations diminished or become insignificant. This suggests that the constellation of behaviors that includes the use of cannabis, alcohol, and other substances might be all play roles in the risk for bipolar disorders, with those different roles being difficult to disentangle. See Box 12-1 for additional discussion on the complex relationship between substance use and mental health disorders.

**CONCLUSION 12-3** There is limited evidence of a statistical association between cannabis use and the likelihood of developing bipolar disorder, particularly among regular or daily users.

[9] The NESARC is a longitudinal and nationally representative survey. Data on psychiatric disorders and quality of life were assessed from two waves of subjects. Wave 1: 2001–2002; n = 43,093, Wave 2: 2004–2005; n = 34,653.

[10] Cougle et al. (2015) and Feingold et al. (2104) used the same dataset, but they chose to use different outcome variables: one analyzed past-year cannabis use, while the other examined past- year weekly cannabis use.

## Is There an Association Between Cannabis Use and the Course or Symptoms of Bipolar Disorder?

*Systematic Reviews*

The committee identified Gibbs et al. (2015) as a systematic review that assessed the relationship between cannabis use and the course, symptoms, or other endpoints in individuals with bipolar disorder. Gibbs et al. (2015) concluded, based on their narratives of three studies, that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases.Their narrative summarizes the findings of the three studies: the duration of active cannabis use was associated with duration of mania syndrome/symptoms; cannabis use within a quarter (3-month time period) was associated with manic symptoms or episodes; and a report of "any cannabis use" was associated with mania symptoms over 1 year in a sample of 3,426 in- and outpatients patients. The three studies were published in 2000, 2008, and 2009. The studies used clinical samples of 50 new-onset bipolar patients aged 16–54, 166 first-episode DSM-IV bipolar I patients aged 18–72, and 3,426 bipolar in- and outpatients and outpatients (age not reported). No other information (gender, country, etc.) about the study populations was reported.

*Primary Literature*

Zorrilla and colleagues (2015), using the European Mania in Bipolar Longitudinal Evaluation of Medication study (n = 1,922 patients) showed that previous users of cannabis had similar outcomes to never users (all $p > 0.05$) in terms of bipolar disorders, whereas current users had lower rates of recovery ($p = 0.004$) and remission ($p = 0.014$) and higher rates of recurrence of bipolar disorder ($p = 0.014$). They also demonstrated that the median time to remission was longer in the current cannabis use group (571 days, 95% CI = 539–588) compared with the other two groups (never users: 236 days, 95% CI = 209–345; previous users: 189 days, 95% CI = 1.5–357), while the times to relapse and recurrence were shorter in current use group. Using Cox regression models, Zorrilla and colleagues found that cannabis use (versus no use) was associated with time to recovery (HR, 0.53; 95% CI = 0.298–0.959), relapse (HR, 1.61; 95% CI = 1.116–2.316), and recurrence (HR, 1.67; 95% CI = 1.206–2.320). However, when alcohol and other substance use variables were included in the model as confounders, only the time to recurrence remained significantly associated with cannabis use (HR, 1.47; 95% CI = 1.030–2.092).

Using the NESARC data with two waves, Feingold et al. (2014) examined the relationship between weekly cannabis use and almost daily cannabis use and found a steady association with the incidence of mania/hypomania symptoms in all adjusted models (OR, 2.47; 95% CI = 1.03–5.92). In contrast, daily cannabis use was not associated with mania/hypomania symptoms (OR, 0.52, 95% CI = 0.17–1.55).

*Discussion of Findings*

The evidence on the association between cannabis use and the course and symptoms in patients with bipolar disorder is modest, but it is suggestive that cannabis use moderates the

course of bipolar disorder by increasing the time to recovery, relapse, and recurrence of manic phases. As discussed in the section above, when adjustments for alcohol and other substance use variables are included in the model as confounders, only the time to recurrence remains as significantly associated to cannabis use. There is also moderate evidence that weekly cannabis use to almost daily cannabis use can lead to the onset of mania/hypomania symptoms in adjusted models, but there is less evidence of this association for daily users of cannabis. The authors report that given the inconclusive nature of the relationship between very frequent cannabis use (daily/almost daily) or less than weekly cannabis use and the onset of mania/hypomania symptoms in adjusted models (i.e., dose–response), other factors that have not been identified might mediate the relationship. The authors suggest that part of the problem of being able to find a conclusive relationship between the frequency of cannabis use and mania or hypomania symptoms might be due to the resemblance of mania and hypomania symptoms to psychotic symptoms, making it difficult to discriminate between these types of symptoms. It should also be noted that in some of the studies reviewed above, the analyzed patient populations were undergoing treatment for bipolar disorder, adding an additional layer of limitations to the research findings.

In reviewing the literature on the relationship between cannabis use and bipolar disorder, the committee identified various limitations in the studies discussed above, including a lack of biogenetic covariates that could relate to both cannabis use and bipolar disorders, as well as other psychological symptoms that are not adjusted in these studies. Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which that could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem.

**CONCLUSION 12-4** There is moderate evidence of a statistical association between regular cannabis use and increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders.

## DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, pre-menstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015); and therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

## Is There an Association Between Cannabis Use and the Development of Depressive Disorders or Symptoms?

*Systematic Reviews*

The committee identified two systematic reviews that assessed the association between cannabis use and the risk of developing depressive disorders or symptoms (Lev-Ran et al., 2013; Moore et al., 2007). The most recent systematic review is discussed.

Lev-Ran et al. (2013) searched the published literature through 2012 and included studies with: population-based data that were collected longitudinally and prospectively; an exposure variable referring specifically to cannabis use (not "substance use"); outcome measures that referred specifically to depression (and not, for example, mixed anxiety–depressive symptoms); the outcome variable (depression) controlled for at baseline, or individuals with baseline depression being excluded; and data either presented as odds of developing depression following cannabis use or that allowed the odds ratio (OR) to be calculated. When the authors identified multiple studies reporting on the same population cohort at different time points, only one study (the most recent) reporting on the respective cohort was included. The authors identified 14 studies published between 1977 and 2012. Seven were conducted in the United States, and one each were conducted in Australia, Canada, Colombia, the Netherlands, New Zealand, Norway, and Sweden. Sample sizes ranged from 736 to 45,087, with 10 of the samples having 1,000 or more participants. The ages of patients at cannabis assessment included high school age, subjects ages 12–17 or 12–16, and older groups (18–64). A wide range of measures were used to assess cannabis use: (i.e. any cannabis use in the previous 30 days, any previous cannabis use, cannabis use disorder, cannabis use one or more times per month, any cannabis use in the previous year or heavy use (at least once per week in the previous month), at least five previous occasions of cannabis use or heavy use (at least weekly), any use in the previous 6 months, or than 4 occasions of use per month in a 5-year period). Studies also varied in the definition of comparison groups with some studies contrasting any cannabis use to no cannabis use, and other studies comparing "heavy cannabis use" to a group with some or no cannabis use. Thus, the comparison group (lower level of exposure to cannabis) in the latter studies included non-users, as well as individuals using cannabis less than weekly, or individuals not having a cannabis use disorder. Studies varied in their approaches to adjust for confounding factors, ranging from none to adjustment for more than 20 variables. One half of the studies accounted for other types of substance use and or mental health issues as potential confounders. The analysis showed that cannabis use was associated with a small increase in risk for depressive outcome (pOR, 1.17; 95% CI = 1.05–1.30). The analysis further revealed a dose–response relationship, with a slightly higher OR observed in seven studies comparing heavy cannabis use to non-cannabis users (pOR, 1.62; 95% CI = 1.21–2.16).

*Primary Literature*

Although several primary research studies found a positive association, the confounding factors of polydrug use or unspecified cannabis use made it difficult for the committee to make conclusions on the overall findings (Brook, 2016; Nkansah-Amankra, 2016; Rasic, 2013). Additional studies reviewed provided mixed findings on the association between cannabis use and depression or depressive symptoms (Crane, 2015; Gage, 2015; Silins, 2015; Wilkinson,

2016). A consideration of the confounding factors led to several of these mixed findings. For example, Sillins et al. (2015) published an analysis of interview data from three longitundal studies from Australia and New Zealand. The investigators sought to determine the association between the maximum frequency of cannabis use before age 17 and seven developmental outcomes, including depression. The number of participants varied by the outcome assessed, but ranged from n = 2,537 to 3,765. Because this was an integrated study, the outcomes of depression were assessed by different measures (i.e., Composite International Diagnostic Interview, Clinical Interveiw Schedule, and short-form Depression Anxiety Stress Scale) and at different ages across the three studies. The investigators of this study created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years. Using combined data adjusted for study-specific effects, the investigators found a significant asssociation between adolescent cannabis use and the study's measure of depression (less than month use, OR, 1.12; 95% CI = 1.01–1.25; monthly or more, OR, 1.26; 95% CI = 1.02–1.56; weekly or more, OR, 1.42; 95% CI = 1.03–1.94; daily use OR, 1.59; 95% CI = 1.04–2.42), as well as an apparent potential dose–response relationship. However, after adjusting for relevant covariates in the analysis, this association became insignificant and negligible in size (less than monthly use, aOR, 1.01; 95% CI = 0.85–1.19; monthly or more, aOR, 1.01; 95% CI = 0.72–1.42; weekly or more, aOR, 1.02; 95% CI = 0.61–1.69; daily use aOR, 1.02; 95% CI = 0.52–2.01). The authors noted that the confounding factors spanning the individual's background and functioning as wll as parental and peer factors likely affected the change in the research findings.

*Discussion of Findings*

The evidence reported suggests that cannabis use, and particularly heavy cannabis use, is associated with a small increase in the risk of developing depressive disorders. This evidence is supported by a good quality, recent systematic review that included 10 longitudinal studies with sample sizes between 700 and 45,000. Although the supplemental studies from the primary literature reported mixed findings, the committee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran, 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62; Lev-Ran, 2013) The possible relationship between heavy cannabis use and the development of depressive disorders or symptoms needs to be further explored.

Given that these relationships are associational and not necessarily causal, it is important to note possible alternative explanations for the mixed findings. For example, within the literature, a reverse association between cannabis use and depressive disorders has been documented, and the relationship may be bi-directional (Horwood et al., 2012; Wilkinson et al., 2016). This complex scenario is consistent with the known protective roles of the endocannabinoid system in the control of mood and affect, and with the propensity of cannabinoid receptors to undergo desensitization following prolonged activation. See Box 12-1 for an additional discussion on this topic.

To review the research potential therapeutic effects of cannabis or cannabinoids on major depression disorder, please refer to Chapter 4: Therapeutics.

**CONCLUSION 12-5** There is moderate evidence of a statistical association between cannabis use and a small increased risk for the development of depressive disorders.

### Is There an Association Between Cannabis Use and the Course or Symptoms of Depressive Disorder?

*Systematic Reviews*

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder.

*Primary Literature*

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder, and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

**CONCLUSION 12-6** There is no evidence to support or refute a statistical association between cannabis use and changes in the course or symptoms of depressive disorders

## SUICIDE

Suicide is the act of purposely taking one's own life. It is the 10th most common cause of death in the United States, with an estimated 13 suicidal deaths occur per 100, 000 individuals in the United States, and is often related to mental illness, substance abuse, or a major stressful event (CDC, 2014; MedlinePlus, 2016). Cannabis is widely used for both medical and recreational purposes (Azofeifa et al., 2016), and therefore, there is a public health interest to evaluate the possible association between cannabis use and suicide, suicidal attempts, and suicidal ideation.

### Is There an Association Between Cannabis Use and Suicide, Suicide Attempts, and Suicidal Ideation?

*Systematic Reviews*

Two systematic reviews were identified that assessed the association between cannabis use and suicidal ideation, attempts, and suicide (Borges et al., 2016; Moore et al., 2007). We report here on the most recent one. Borges et al. (2016) conducted a systematic review to address multiple questions concerning acute and chronic cannabis use, suicidal ideation, suicidal attempts, and suicide. The authors reported the databases searched and their search terms, but they did not report the number of citations screened or the reasons for exclusions. The term "any

cannabis use" was defined as: life-time use, use before or at age 15, ever used, any use in past 30 days, or any use in the last year. "Chronic use" was referred to as: cannabis use patterns, symptoms of cannabis use disorder, and heavy cannabis use. "Heavy cannabis use" was defined as: used 40 or more times, DSM-IIIR abuse/dependence, ≥6 times/month, >11 times in past year, >10 times, or daily.

The authors reviewed 12 studies that were relevant to the committee's research question. Their meta-analysis of six studies showed that any cannabis use was associated with an increased risk of suicidal ideation (pOR, 1.43; 95% CI = 1.13–1.83). Similarly, a review of five studies showed that heavy cannabis use was also associated with a larger increase of suicidal ideation (pOR, 2.53; 95% CI = 1.00–6.39). The six studies included in the meta-analysis of any cannabis use and suicide ideation were published between 1997 and 2014 and conducted in Canada, New Zealand, Norway, and the United States (four studies) in populations of male and female young adults or adolescents. The five studies included in the meta-analysis of heavy cannabis use and suicidal ideation were published between 1997 and 2013 and conducted in Canada, New Zealand, Norway, and the United States (two studies) in male and female populations of all age groups.

The authors also assessed another subset of six studies to determine the association between any cannabis use and suicide attempts, reporting a pooled odds ratio of 2.23 (95% CI = 1.24–4.00). The studies used reported on male and female adolescents or young adults in Canada, Ireland, and the United States (four studies). A review of a third subset of six studies found a higher risk of suicide attempt associated with heavy cannabis use (pOR, 3.20; 95% CI = 1.72–5.94). These six studies reported on male and female adolescents, young adults, or adults in Canada, New Zealand/Australia (two studies), Norway, and the United States (two studies).

The researchers reported that any cannabis use was associated with an increased risk of death by suicide (pOR, 2.56; 95% CI = 1.25–5.27), based on a meta-analysis of four non-overlapping studies. The studies included two case-control studies and two longitudinal studies published between 2003 and 2012 which were conducted in the United States, Colombia, Denmark, and Sweden; the studies were carried out in young adults and in all age groups, in males and females, and in male-only study groups. Interestingly, the one study restricted to males only showed no association of cannabis with suicide, but the other studies, which used mixed groups of males and females, did show an association of cannabis with suicide.

*Primary Literature*

The committee identified one recent primary article published in 2016 (Shalit et al., 2016) that reported on the association between cannabis use and the risk of suicidality (suicidal ideation and suicide attempt). Shalit and collaborators presented their results using a general population sample of the NESARC (n = 34,653; 963 cannabis users versus 30,586 non-users). They found that in the general population, any cannabis use in Wave 1 (baseline) was not statistically significantly associated with increased risk for developing suicidality in Wave 2 (follow-up) (aOR, 1.56; 95% CI = 0.98–2.46). However, when the results were stratified by gender, the researchers found significant differences in risk for suicidality. Among men, any cannabis use was significantly associated with the incidence of suicidality in fully adjusted models (aOR, 1.91; 95% CI = 1.02–3.56) but not for women (aOR, 1.19; 95% CI = 0.64–2.20). The magnitude of the relationship with the 3-year incidence of suicide ideation is larger in men (aOR, 4.28; 95% CI = 1.32–13.82) who are daily cannabis users, but this pattern is not observed

for women (aOR, 0.75; 95% CI = 0.28–2.05). However, in adjusted models neither cannabis use (aOR, -1.91; 95% CI = 0.85–4.28), nor daily cannabis use (aOR, 1.13; 95% CI = 0.42–3.05) was statistically significantly associated with the incidence of suicide attempts. Another finding of importance was that sex moderated the association between cannabis use, particularly daily use, and suicide attempts, with a significantly increased dose–response relationship in men (any cannabis use OR, 3.35; 95% CI = 1.07–10.47; daily cannabis use OR, 32.31; 95% CI = 2.59–402.88). However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicidal attempts without these symptoms. Other limitations include the use of dichotomous response categories for suicidality when there is some evidence that additional changes to the measures are needed, the lack of adjustment for some early traumatic life events associated with suicidality, and the lack of adjustments for psychotic disorders.

*Discussion of Findings*

The evidence reported suggests that any cannabis use is related with increased suicidal ideation, augmented suicide attempts, and greater risk of death by suicide. The studies presented demonstrate evidence of a dose–response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts. Additionally, sex differences emerged from the research findings related to suicidality (Shatit et al., 2016) and death by suicide (Borges, 2016). These sex differences may have occurred due to differences in where the study samples were recruited (e.g., Australia, Canada, Denmark, New Zealand, Norway, Sweden, United States, etc.) or how the data were assessed. This might suggest that sample composition, gender, and the type of assessment could matter when examining these associations between cannabis use and suicidality and suicide completion.

Although the evidence seems to support a relationship between cannabis use and suicidality, particularly heavy cannabis use and suicidality, the limitations of the literature temper such findings. Several limitations should be noted including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose–response analyses, and problems of small sample size. Additionally, as reported by the authors, some studies adjust for alcohol and other comorbidities, while in other studies there is no report of such adjustments. There is a strong need for new studies that to discriminate between the acute and chronic use of cannabis and between suicidal ideation, suicide attempts and completed suicides.

**CONCLUSION 12-7**

**12-7(a)** There is moderate evidence of a statistical association between cannabis use and increased incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users.

**12-7(b)** There is moderate evidence of a statistical association between cannabis use and increased incidence of suicide completion.

## ANXIETY

Anxiety disorders share features of excessive fear and anxiety, which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the United States adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood regulation, it is worthwhile for this report to explore the relationship between anxiety and cannabis.

### Is There an Association Between Cannabis Use and the Development of Anxiety Disorders?

*Systematic Reviews*

One systematic review was identified that assessed the relationship between cannabis use and anxiety disorders (Kedzior and Laeber, 2014). The authors searched two databases for articles published through 2013 to identify studies that had been conducted in non-institutionalized populations, with anxiety diagnoses based on DSM/ICD criteria, with odds ratios or data sufficient for the calculation of effects, and with comparison data from healthy non-users. They then identified five studies that examined cannabis use at baseline and anxiety at follow-up. The five studies were all longitudinal, published between 1996 and 2013, and conducted in Australia, Colombia, the Netherlands, New Zealand, and the United States. Sample sizes were more than 2,000 or greater in four studies and over 12,000 in the fifth study. Four studies were of adolescents and a fifth studied the general population (age unspecified). The five studies adjusted for confounders such as demographics, prior anxiety disorder diagnosis, alcohol and tobacco use, and other mental health problems at age 15. In their review of the five studies, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the developmment of symptoms of anxiety at follow up (OR, 1.28; 95% CI = 1.06–1.54), after adjusting for confounders (e.g., other substance use, psychiatric comorbidity, certain demographics).

*Primary Literature*

In a longitudinal U.S. study of a nationally representative sample of adults 18 years or older (NESARC; n = 34,653), Blanco and colleagues (2015) investigated the prospective associations of cannabis use in the past 12 months (Wave 1; years 2001–2002) with anxiety disorders 3 years later (Wave 2; years 2004–2005) and adjusted for socio-demographic characteristics, family history of substance use disorder, disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and respondent's history of divorce. The researchers found that cannabis use in the 12 months preceding the survey was not associated with an increased prevalence of anxiety disorders (OR, 1.0; 95% CI = 0.8–1.2) after adjustments for covariates. The researchers also reported no significant relationship of cannabis use (Wave 1) with the prevalence of panic disorder (OR, 0.8; 95% CI = 0.5–1.2), social anxiety disorder (OR, 1.2; 95% CI = 0.8–1.8), specific phobia (OR, 0.9; 95% CI = 0.7–1.2) or generalized anxiety disorder (OR,

1.0; 95% CI = 0.7–1.4) assessed 3 years later (Wave 2). The researchers also found no significant relationship between cannabis use and incident anxiety disorders (aOR, 0.9; 95% CI = 0.7–1.1). However, they did find that an increased frequency of cannabis use was related with significantly increased odds of incident social anxiety disorder (OR, 1.8; 95% CI = 1.1–2.8). Some of the limitations of this study are that cannabis use was ascertained by self-report, causality could not be established because of the possibility of residual confounding, and the follow-up period was limited to 3 years.

Feingold and colleagues (2016) used the same dataset as Blanco et al. (2015), NESARC, and also found no association of cannabis use with the increased incidence of any anxiety disorder (aOR, 1.12; 95% CI = 0.63–0.98), after adjusting for covariates. However, they did find a statistically non-significant association between daily or almost daily use of cannabis at Wave 1 (baseline) with the incidence of social anxiety at follow-up 3 years later (aOR, 1.98; 95% CI = 0.99–6.98). This relationship was found to be significant in older adults (aOR, 2.83; 95% CI = 1.26–6.35) but not for younger adults (aOR, 1.76; 95% CI = 0.44–6.98). They also found a significant relationship between cannabis use disorder at baseline and incident social anxiety disorder among young adults (aOR, 2.45; 95% CI = 1.19–5.06) but not older adults (aOR, 1.38; 95% CI = 0.58–3.25). No other associations between cannabis use disorder and other anxiety disorders proved to be significant after adjustment for covariates.

Cougle et al. (2015) also used the NESARC to examine past-year regular cannabis use (defined as at least weekly use) and current and prospective presence of anxiety disorders 3 years later. These authors found no association (OR, 1.09; 95% CI = 0.90–1.32) in the prospective analyses that adjusted for psychiatric comorbidity and sociodemographic factors. However, when looking at specific anxiety disorders, Cougle and colleagues report finding a relationship between regular cannabis use and an increased risk of developing panic disorder with agoraphobia (OR, 1.56; 95% CI = 1.11–2.19) and social phobia (OR, 1.89; 95% CI = 1.54–2.32). As with other studies using the NESARC, the authors emphasize the non-randomized nature of the study design, the possibility that the study was underpowered to find certain relationships and the relatively short time period of observation.

Bechtold and colleagues (2015), using data from the oldest cohort of the Pittsburgh Youth Study, found that there were no differences among cannabis trajectory groups (categorized as low/non-users, adolescence-limited users, increasing users, and early onset chronic users) related to a lifetime diagnosis of anxiety disorders for black or white men after controlling for confounders (i.e., socioeconomic status, co-occurring use of other substances, physical and mental health problems that predated cannabis use, and access to medical care). In this study cannabis use was evaluated with the Substance Use Questionnaire, with respondents (who were from ages 15 to 26) initially indicating the number of days they had used cannabis in the previous 6 months and then, in each of the subsequent 10 annual follow-ups, reporting their use in the previous year. At age 36, respondents were assessed with the Diagnostic Interview Schedule to determine whether they had ever met the criteria for an anxiety disorder, and an analysis shows that the patterns of cannabis use from adolescence to young adulthood were not related to anxiety disorders. However, the authors mentioned several limitations, including the possibility of selection effects, the fact that cannabis use was determined by self-report, and the use of a limited sample that used cannabis from one geographic area and only included white and black men, implying that the results might not be generalizable to the general population. A recent study by Gage and colleagues (2015) found similar results. Using data from the Avon Longitudinal Study of Parents and Children (a UK birth cohort study), they found no evidence of

an association between cannabis use at age 16 and anxiety disorder at age 18 (aOR, 0.96; 95% CI = 0.75–1.24) after adjusting for pre-birth and childhood confounders (family history of depression, maternal education, urban living, IQ, borderline personality traits, victimization, peer problems, conduct disorder, and other substance use). The authors cite as limitations of their study the use of self-reported data, poor follow-up rates, and a limited power to detect small effects.

Brook and colleagues (2014), using the Harlem Longitudinal Developmental Study, assessed urban African American and Puerto Rican participants (n = 816) with four waves of data. In this study, Brook et al. (2014) found that participants with joint chronic cannabis, tobacco, and alcohol use were at an increased risk for generalized anxiety disorder in adulthood when compared to those with occasional alcohol use and no smoking and no cannabis use (OR, 4.35; 95% CI = 1.63–11.63). Again, this study had such limitations the use of self-reports, the use of proxies to determine earlier generalized anxiety disorder (depression in Time 1), and omitted variables (such as family substance use) that could have explained such relationships.

Additional work by Brook and colleagues (2016) reported on a large community-based sample (the Children and Adults in Community study, n = 973 at Time 1), examining comorbid trajectories of substance use which included conjoint chronic cannabis with chronic alcohol and cigarette use as predictors of generalized anxiety disorder. According to their multivariate logistic regression analyses, the Bayesian posterior probability (BPP) of members who were chronic or moderate to heavy users of cannabis, alcohol, and cigarettes, when compared to the patterns of those with occasional alcohol use and no smoking and no cannabis, had an adjusted odds ratio of 6.39 (95% CI = 2.62–15.56). This suggests that the conjoint use of cannabis with alcohol and cigarettes could have biological or psychosocial effects that increased the risk for generalized anxiety disorder. However, the study had several limitations in the present study, including having a mostly white sample from upstate New York and not including environmental or social variables that could explain the relationship under study such as family substance use or childhood psychiatric disorders.

*Discussion of Findings*

Studies examining the relationship between cannabis use and anxiety disorder show mixed results depending on whether they assessed the development of anxiety symptoms or the incidence of anxiety disorders, whether the explanatory variable was any cannabis use or cannabis use disorder, and whether there were adjustments for psychiatric comorbidity and sociodemographic factors. For example Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up. In contrast, the 2015 report by Blanco and colleagues, the 2015 report by Cougle et al., and the 2015 report by Gage and colleagues all found no association between cannabis use and an increased prevalence of anxiety disorders in adjusted models. However, both Feingold and Blanco's studies did find an association of daily or almost daily use of cannabis at Wave 1 with the incidence of social anxiety disorder at follow-up 3 years later. Age seemed to moderate this relationship since it was found to be significant in older adults, but not in younger adults.

Some of the limitations of these studies are that cannabis use was ascertained by self-report, that causality cannot be established because of the possibility of residual confounding, that the follow-up period was limited to 3 years, and that there was a high loss in the follow-up and limited power to detect small effects. Further work needs to be done to examine why the

outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder. Morever, studies are needed to determine whether psychiatric comorbidity, sociodemographic factors, or the conjoint use of cannabis with alcohol and cigarettes have biological or psychosocial effects that increase the risk for generalized anxiety disorder.

To review the research potential therapeutic effects of cannabis or cannabinoids on anxiety, please refer to Chapter 4: Therapeutics.

**CONCLUSION 12-8**

**12-8 (a)** There is limited evidence of a statistical association between cannabis use and the development of any type of anxiety disorder, except social anxiety disorder.

**12-8 (b)** There is moderate evidence of a statistical association between regular cannabis use and increased incidence of social anxiety disorder.

### Is There an Association Between Cannabis Use and the Course or Symptoms of Anxiety Disorders?

*Systematic Reviews*

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints of anxiety disorders.

*Primary Literature*

Recent work by Grunberg and collaborators (2015) conducted a prospective study to examine whether cannabis use (i.e., use during the past 30 days using the Time-Line Follow Back[11]) moderates the effects of temperament on the level of anxiety symptoms (measured with Achenbach's System of Empirically Based Assessment) within late adolescence and early adulthood (n = 338; 18 to 21-year-olds). While there was no association between cannabis use groups and anxiety symptoms among the college students in this prospective study, the researchers conducted simple slope analyses investigating the relationship between harm avoidance (characterized by heightened apprehension, shyness, pessimism, and inhibition of behaviors) and prospective anxiety symptoms for those subjects who rated low (zero days of use out of 30 days) and high (approximately 26 days of use out of 30 days) on cannabis use. The researchers found that harm avoidance measured at baseline was associated with more symptoms of anxiety measured a year later—but only for those low in cannabis use ($\beta = 0.15$, $t(329) = 2.69$, $p < 0.01$). When cannabis use was high, harm avoidance was unrelated to anxiety ($\beta = -0.14$, $t(329) = -1.40$, $p = 0.16$). Study participants with higher cannabis use showed a positive association between novelty seeking and anxiety symptoms ($\beta = 0.28$, $t(329) = 3.46$, $p = 0.001$) ,

[11] Authors describe this as a calendar-assisted structured interview that allows participants to indicate the amount of cannabis used on each day over the past month.

while those lower in cannabis use showed no relation between novelty seeking and anxiety symptoms ($\beta = -0.08$, $t(329) = -1.61$, $p = 0.11$).

*Discussion of Findings*

Grunberg and collaborators (2015) warned however, that the findings discussed above should be taken with caution since the mechanisms underlying these relations are still not clear. In addition, although this study uses a prospective design in which cannabis use and temperment are evalutated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site. The authors emphasized that the reason that the relationship between cannabis use and anxiety symptoms is inconsistent is that there was no consideration of cannabis effects on other factors that influence anxiety symptoms such as temperament (i.e., levels of harm avoidance and novelty seeking) within the sample. Some limitations of this study are the use of a college student sample, the use of self-report for all assessments, and the use of correlational data although cannabis use and temperament were measured 1 year before anxiety symptoms. Given the limited evidence of studies that addrdess the realtionship between cananbis use and anxiety symptoms, these findings need to be replicated in larger samples with appropriate controls.

**CONCLUSION 12-9** There is limited evidence of a statistical association between near daily cannabis use and increased symptoms of anxiety.

## POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the DSM-V. The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2015, pp. 271–272). Given the known psychoactive effects of cannabis, the committee chose to explore the association between PTSD and cannabis use in this review.

### Is There an Association Between Cannabis Use and the Development of PTSD?

*Systematic Reviews*

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the risk of developing PTSD.

*Primary Literature*

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the development of PTSD and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

**CONCLUSION 12-10** There is no evidence to support or refute a statistical association between cannabis use and the development of posttraumatic stress disorder.

### Is There an Association Between Cannabis Use and the Course or Symptoms of PTSD?

*Systematic Reviews*

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints in PTSD.

*Primary Literature*

Gentes et al. (2016) found that past 6-month cannabis use was associated with increased PTSD severity (Clinician Administered PTSD Scale; global severity score; aOR, 1.30; 95% CI = 1.01–1.66), depressive symptoms (Beck Depression Inventory; aOR, 9.25; 95% CI = 1.13–1.75), and suicidality (Beck Depression Inventory Item 9; aOR, 4.63; 95% CI = 1.02–1.54) in a population of treatment-seeking veterans (n = 719). In this study, the odds ratios were adjusted for age, race, service era, and combat exposure, but not co-occurring substance use. Conversely, Manhapra et al. (2015) found improvements in PTSD symptoms (Mississippi Scale for Combat-Related Posttraumatic Stress Disorder), violence, and suicidality after 4 months of abstinence from cannabis relative to symptoms upon entry to the study in a large population of veterans admitted for an intensive PTSD program (n = 22,948). Villagonzalo et al. (2011), in a small study of patients (n = 80; mean age 35 years) participating in a methadone maintenance program, found that the severity of cannabis use was associated with the occurrence of certain PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist–Civilian Version. Significant findings were identified for measures of re-experiencing (i.e., repeated disturbing dreams, $\chi^2$ (2) = 6.351; p <0.05; physical reaction at reminder of event $\chi^2$(2) = 7.053; p <0.05), hyperarousal (i.e., difficulty concentrating, $\chi^2$(2) = 7.517; p <0.05; "super alert" $\chi^2$(2) = 6.778; p <0.05; easily startled $\chi^2$(2) = 9.645, p <0.01), and overall PTSD symptoms (1-way ANOVA, F(2,65) = 3.705; p <0.05).

Of interest, the committee also identified two large observational studies that compared the effects of cannabis to controls. Both studies enrolled predominately male veterans. A large cohort study (Wilkinson et al., 2015) examined outcomes for 2,276 veterans who received specialized intensive PTSD services between 1992 and 2011. Assessments for substance use and PTSD symptoms were taken at intake and at 4 months after discharge. Veterans who continued to use or started using cannabis after discharge had significantly worse PTSD symptoms and greater drug abuse than those who had never used or who had stopped cannabis use at 4 months after discharge (p <0.0001). Starters also had more violent behavior in the 4 months after

enrollment compared to other groups ($p < 0.0001$). There were no significant differences among the groups on employment status. A second study (Johnson et al., 2016), was a matched, case-control, cross-sectional study that was conducted in 700 veterans with probable PTSD, half of whom used cannabis and half who were non-users. Cannabis users and non-users did not differ on PTSD symptom severity ($p = 0.91$) or depression severity ($p = 0.07$), as measured by the PTSD Checklist-Civilian version and the Patient Health Questionnaire, respectively. However, cannabis users were more likely to experience suicidal ideation ($p = 0.04$) and reported more alcohol use ($p < 0.001$), as measured by the Paykel questionnaire, an alcohol Timeline Follow-back assessment, and the Alcohol, Smoking, and Substance Involvement Screening Test.

*Discussion of Findings*

Notable in this section relative to the others in this chapter is the lack of data addressing the key questions posed by the committee. For example, using the committee's specified search strategy, we found no relevant studies directly addressing the question of whether cannabis use is associated with an increased risk of PTSD. Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies, and that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn. Overall, there is limited evidence for an association between cannabis use and increased PTSD symptom severity. The direction of the association is difficult to address, however. It has been argued that PTSD is a risk factor for cannabis use, and cannabis-using patients with PTSD often cite symptom-coping motives for cannabis use, suggesting that more severe PTSD may be driving patients to increase cannabis use in an effort to self-medicate.[12] In contrast, one study (Manhapra et al., 2015) found overall improvements in several symptom domains after 4 months of abstinence from cannabis, suggesting that cannabis use may be causally related to more severe PTSD symptoms. See Box 12-1 for a discussion on why it is often difficult to conclude causality in the associations between substance use and mental health.

To review the research potential therapeutic effects of cannabis or cannabinoids on PTSD, please refer to Chapter 4: Therapeutics.

**CONCLUSION 12-11** There is limited evidence of a statistical association between cannabis use and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder.

**BOX 12-2**
**Special Considerations for**
**Systematic Reviews of Observational Studies**

The quality assessment of the systematic reviews in this chapter followed the research methods used throughout this report, within the context of the mental health literature. Of note,

[12] Studies examining PTSD as a risk factor for cannabis use and cannabis use disorders were identified and are discussed in Chapter 13 of this report.

the primary literature in mental health is mostly observational (in contrast to the literature base in other fields, such as therapeutics), and it was not possible to restrict systematic reviews and meta-analyses to those that synthesized evidence from randomized clinical trials (RCTs). Accordingly, the vast majority of the studies included in the systematic reviews and meta-analyses summarized in this chapter were observational studies. In addition to receiving a lower-quality grading in most systems, the methodologic science around the synthesis of observational data is less developed than it is for RCTs. The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising out of the greater variety in study design and conceptualization and the fact that there has been generally less experience in applying the methodology of systematic reviews and meta-analysis to observational literature. For example, none of the systematic reviews discussed in this chapter mentioned a protocol, an ethics review board, or a priori published research objectives, features that have become increasingly standard in systematic reviews of RCTs. Mallen and colleagues (2006, p.765) noted, "Quality assessment does not routinely occur in systematic reviews of observational studies. Where it does occur, there is no clear consensus in the method used." Brugha and colleagues (2012, p.450), in their review of systematic reviews and meta-analyses of observational psychiatric epidemiology studies, found "a number of deficiencies in the conduct and reporting of systematic reviews and meta-analyses of observational psychiatric epidemiology studies that could have serious implications for inferences drawn or decisions made on the basis of these reviews. There were frequent omissions of descriptions of method of abstraction, study quality, publication bias, bias and confounding."

In assessing the body of evidence, it is tempting to correlate the number of systematic reviews with the strength of the evidence; however, a number of concerns arise when synthesizing evidence across systematic reviews. When multiple systematic reviews address similar research questions or slight variations on similar research questions, it is likely that the reviews will include some of the same primary studies. For example, in the Schizophrenia section above, the three systematic reviews assessing the effects of cannabis on cognition—Donoghue and Doody (2012), Rabin et al. (2011), and Yucel et al. (2012)—each cite the primary study by Schnell et al. (2009). Another four studies were included in two of the systematic reviews on cognition. Given the use of some primary studies in more than one systematic review, the number of systematic reviews or meta-analyses may not, by themselves, indicate a stronger body of evidence.

While it is easy to understand how multiple reviews might identify similar studies, it is also of concern when reviews identify different studies. For example, the systematic review on cognition by Rabin et al. (2011) identified four studies that were not included in the reviews by Donoghue and Doody (2012) or by Yucel et al. (2012), and Yucel and colleagues (2012) also identified four studies that were not included in the other systematic reviews. This may be explained by a careful examination of the search strategies and inclusion/exclusion criteria, but the reasons for such differences are not always transparent.

Exposure measurement is always of concern in observational studies, and assessment of cannabis exposure is particularly fraught because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific chemicals, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. For example, systematic

reviews may include studies using greatly differing definitions such as non-dependent cannabis use in past week, a history of 0.5 g cannabis/day, cannabis use in the last 6 months, and >2g cannabis/week (Rabin et al., 2011). In addition, studies focusing on mental health may use medical records showing a diagnosis of cannabis use disorder as their exposure variable, either focusing on the disorder as a construct or as a proxy for cannabis exposure. This last approach allows researchers to consider the construct of cannabis use disorder, but it may result in exposure and non-exposure groups having similar intakes of cannabis. One can imagine a scenario where a person with a cannabis use disorder diagnosis has perhaps not consumed cannabis in the preceding week, month, or other time frame and where individuals without a diagnosis of cannabis use disorder had consumed cannabis in the same time frame. In this scenario, misclassification in both directions would result in biases towards the null, although differences between individuals with and without mental health diagnoses of cannabis use disorder could be expected to be associated with other differences observed in the study groups.

## RESEARCH GAPS

As noted above, we found a paucity of studies relevant to our key questions. To address the research gaps relevant to PTSD, the committee suggests the following:

- More longitudinal studies to determine whether cannabis use is associated with an increased incidence of PTSD.
- In patients with PTSD, current data do not provide a very clear picture as to whether cannabis use affects PTSD symptoms. More longitudinal studies examining the effects of cannabis use on PTSD symptoms need to be conducted, with a specific emphasis placed on detailed measures of cannabis use (amounts, potency, routes of administration), controls for baseline symptom severity and the use of other substances, and temporality (excluding patients with cannabis use at study entry).
- From a cannabis therapeutics perspective, blinded, randomized, placebo-controlled studies in patients with PTSD need to be conducted to evaluate any potential therapeutic benefits of cannabis on PTSD symptoms and course.
- There is also a research need to investigate cannabis and cannabis constituents (tetrahydrocannabinol and cannabidiol) in animal models.

## SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the association of cannabis use with prioritized mental health conditions. The health conditions reviewed in this chapter include: schizophrenia and other psychotic disorders; bipolar disorder; depression; suicide; anxiety; and posttraumatic stress disorder (PTSD). The committee formed a number of research conclusions related to these health endpoints; however, it is critically important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections. See Box 12-3 for a summary list of the chapter's conclusions.

A conclusion weighted as substantial was reached for the research question addressing the statistical association between cannabis use and the development of schizophrenia or other psychoses. As noted in the chapter's Discussion of Findings sections, there are common trends in the types of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups), variable analysis of cannabis use (i.e., dose/amount/frequency current versus. lifetime), small sample sizes, and research gaps in the studies of depression and PTSD. These limitations highlight the enormous amount of available opportunity to advance the current research agenda, in the hopes of providing comprehensive and conclusive conclusions on the potential therapeutic benefits and harms of cannabis or cannabinoid use.

**BOX 12-3**
**Summary of Chapter Conclusions***

**There is substantial evidence of a statistical association between cannabis use and:**

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

**There is moderate evidence of a statistical association between cannabis use and:**

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

**There is moderate evidence of *no* statistical association between cannabis use and:**

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

**There is limited evidence of a statistical association between cannabis use and:**

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

**There is no evidence to support or refute a statistical association between cannabis use and:**

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

* Numbers in parentheses correspond with chapter conclusion number.

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NEWS

# Cannabis use in psychotic patients is linked to worse outcomes

Jacqui Wise

London

Cannabis use among patients with first episode psychosis is associated with substantially worse clinical outcomes, a large study published in *BMJ Open* has found.[1]

Psychotic patients with a history of cannabis use were more likely to be admitted to hospital, to require compulsory admission, and to spend an extra 35 days in hospital in the five years after their first episode, the study found. Cannabis use was also linked to prescription of several different antipsychotic drugs during the follow-up period, suggesting treatment failure.

The five year study included 2026 people with first episode psychosis who were accepted by an early intervention service in the South London and Maudsley NHS Foundation Trust, one of the largest providers of mental health services in Europe. Cannabis use was noted in the records of 46.3% of patients using the intervention services within a month of starting treatment and was particularly common in single men aged 16 to 25.

Its use was associated with a 50% higher frequency of hospital admissions (incidence rate ratio 1.50 (95% confidence interval 1.25 to 1.80)). Users had an average of 1.8 admissions in the five years after the first service visit, compared with an average of 1.2 admissions among non-users in the same period.

The drug was also associated with increased odds of compulsory detention under the Mental Health Act: 45% in those who used cannabis, compared with 34% in those who did not (odds ratio 1.55 (1.16 to 2.08)).

The study also linked cannabis use to a greater number of days spent in hospital, significant from year two onwards. The length of stay increased from an average of 21 extra days within three years to 35 extra days within five years among cannabis users.

And cannabis use was linked to an increased likelihood of being treated with clozapine and to a higher number of prescriptions for different antipsychotics. The number of unique antipsychotics prescribed ranged from 0 to 11.

The researchers said that they could not establish whether patients were resistant to a given antipsychotic or whether their prescription had been changed to a new drug because of relapse or side effects. However, they said that this suggested an association between cannabis use and increased risk of hospital admission linked to treatment failure.

They added that, as the study was observational, no firm conclusions could be drawn about cause and effect. But they concluded that their findings "highlight the importance of ascertaining cannabis use in people receiving care for psychotic disorders and prompt further study to investigate the mechanisms underlying poor clinical outcomes in people who use cannabis, and strategies to reduce associated harms."

1 Patel R, Wilson R, Jackson R, et al. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. *BMJ Open* 2016; doi:10.1136/bmjopen-2015-009888. .

## Figure

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# Marijuana Violence and Law

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**Abstract**

Marijuana is currently a growing risk to the public in the United States. Following expanding public opinion that marijuana provides little risk to health, state and federal legislatures have begun changing laws that will significantly increase accessibility of marijuana. Greater marijuana accessibility, resulting in more use, will lead to increased health risks in all demographic categories across the country. Violence is a well-publicized, prominent risk from the more potent, current marijuana available.

We present cases that are highly popularized storylines in which marijuana led to unnecessary violence, health risks, and, in many cases, both. Through the analysis of these cases, we will identify the adverse effects of marijuana use and the role it played in the tragic outcomes in these and other instances. In the analysis of these cases, we found marijuana as the single most common, correlative variable in otherwise diverse populations and circumstances surrounding the association of violence and marijuana.

**Keywords:** Marijuana; Bullying behaviour; Aggression; Intoxication; Cannabis use

## Cases Reports

Michael Brown robbed a convenience store for a large box of cigarillos to smoke marijuana and assaulted the store clerk. Subsequently, the 18 year old Brown attacked police officer Darren Wilson without provocation, punching him in the face through the window of his police car, and attempting to grab his gun. Wilson shot and killed Brown as he tried to escape in a very agitated, paranoid, confused and aggressive state. Along with the cigarellos, marijuana was found in Brown's system at the time of death [1].

Trayvon Martin was shot and killed by George Zimmerman, a neighborhood watch volunteer. Marijuana was found in Martin's system the night he was shot [2]. He also had been suspended from school for possession of marijuana.

Laquan McDonald slashed a tire and damaged a police car. After ignoring verbal instruction to drop the knife, he was shot sixteen times. McDonald had used marijuana every day since the age of 10 or 11 years old [3].

Deven Guilford was shot and killed by a policeman during a traffic stop after becoming assaultive. He was a known marijuana user as he professed his "love" for marijuana on social media [4].

Freddie Gray fell into a coma while being transported after an arrest for possession of an illegal switchblade. At the time of his death, Gray tested positive for marijuana and heroin. Gray had multiple prior charges for marijuana possession [5].

Lakeisha Holloway drove her car onto a sidewalk on the Las Vegas strip, killing one and injuring over thirty-five others [6,7]. The toxicology exam illustrated that Holloway had marijuana in her system at the time of the vicious attack [8].

Robert Lewis Dear shot three people and injured nine others at a Planned Parenthood Clinic in Colorado Springs, Colorado. He was a marijuana user and illustrated mental health issues [9].

Joseph Jesse Aldridge found his mother dead of natural causes and went on a shooting rampage, killing seven people and himself. In 2008, Aldridge had pled guilty to federal charges of possessing firearms while using marijuana. He was required to complete mental health and substance use counseling for marijuana [10].

Jared Lee Loughner shot Arizona Congresswomen Gabrielle Gifford and eighteen other, killing six. He was arrested in 2007 for marijuana possession and other paraphernalia. Friends and classmates knew him as a marijuana user. He was also diagnosed with paranoid schizophrenia [11].

The Tsarnaev brothers killed three and injured 264 others with bombs at the Boston Marathon on April 5, 2013. Friends say they were both heavy marijuana users. The wife of the older brother, Tamerlan, described a change in his attitude as he became violent toward her with his increasing marijuana use [12].

A Dearborn Heights man plotted ISIS attacks on church. In an affidavit filed in a criminal complaint on weapons and marijuana charge, Khalil Abu-Rayyan is described as being an ISIS supporter who talked about committing violent acts of terrorism, including shootings and beheadings [13].

Osama bin Laden became paranoid and obsessive in the days prior to his death. High-strength marijuana plants were found within bin Laden's compound in Pakistan [14].

## Studies Show an Association between Marijuana and Mental or Physical Consequences

### Studies show violence and aggression with marijuana use

Marijuana intoxication results in panic reactions and paranoid feelings whose symptoms lead to violence [15]. The sense of fear, loss of control, and panic is associated with violence [16-18]. Also marijuana use increases heart rate, which may be associated with violent behaviour [19-22].

When people stop using marijuana they may experience a variety of withdrawal symptoms, including sleep disturbance, irritability or restlessness, loss of appetite, anxiety, and sweating [23,24]. Experiencing any of these symptoms can make a person angry, ranging from mild irritation to violent rage. Marijuana withdrawal can lead to intimidating violent or bullying behavior, endangering the perpetrator or other people and property [25].

In incarcerated subjects, studies found that one-third of the subjects that committed homicide had used marijuana twenty-four hours before the homicide. Further, three-quarters of those subjects were experiencing at least one mental or physical effect from marijuana intoxication when the homicide occurred.

Similarly, individuals in remote Aboriginal Australian Communities who reported current cannabis use were nearly four times more likely than nonusers to present at least once for violent trauma. Homicide offenses have been repeatedly documented to be connected to drug use, and marijuana is often one of those drugs [26].

Marijuana use is also indicative of intimate partner violence [27]. Consistent use of marijuana during adolescence was the most predictive indicator of intimate partner violence [28]. Also, marijuana use during adolescence was associated with perpetration or both perpetration and victimization by an intimate partner in early adulthood [29].

There is also a positive association between peer victimization and cannabis use in adolescents. Cannabis use is likely to be associated with perpetrator victims, those who initiate violence while using marijuana and experience retaliation to their aggressive acts. This trend suggests that cannabis use might be strongly related to outward aggression by the user [30].

Cannabis use also increases an adolescent's own likelihood of being victimized by peers. In particular, mental effects of cannabis have the potential to decrease the ability to accurately identify, evaluate, or avoid potentially dangerous persons or situations [25].

### Studies show psychosis and paranoia

Cannabis intoxication leads to acute psychosis in many individuals and can produce short-term exacerbations of pre-existing psychotic diseases [31-34]. Cannabis use also causes symptoms of depersonalization, fear of dying, irrational panic and paranoid ideas which coincide with acute intoxication and remit quickly [35].

It was reported that 15% of cannabis users identified psychotic-like symptoms, the most common being hearing voices or having unwarranted feelings of intimidation and persecution or paranoid thoughts [36].

The potency of the marijuana has varying effects on users. A study analyzed the proportion of patients in South London with first episode psychosis attributable to high-potency cannabis use and found that the use of high-potency cannabis (skunk) confers an increased risk of psychosis compared with traditional low-potency cannabis (hash) [37].

The risk of individuals having a psychotic disorder showed a roughly three times increase in users of skunk-like cannabis (high-potency) compared with those who never used cannabis. Use of skunk-like cannabis everyday conferred the highest risk of psychotic disorders compared with no use of cannabis [6]. Potency in these studies is similar to marijuana currently available in the U.S. Direct administration of cannabis resulted in predictable increased occurrence of paranoia in comparison to those who received placebo.

Epidemiological studies showed that cannabis is the most frequently used drug among those diagnosed with bipolar disorder [5]. Studies have also shown that as the frequency of cannabis use increases, so does the risk for psychotic disorders, such as schizophrenia [38]. The investigators of Schizophrenia Commission concluded that cannabis use is the most preventable risk factor for psychosis [39-44]. High proportions of persons with schizophrenia report regular cannabis use and meet criteria for cannabis use disorder [45].

Findings suggest that activity in the basal lateral medulla is involved in marijuana-induced paranoia (state of becoming afraid of things that would normally trigger fear) [44]. That means marijuana is actually enhancing type of learning about fear, leading the brain to jump to conclusions about the mild experiences, perceiving them as scarier as and more strongly connected to other scary situations than they are. This marijuana induced fear-based learning helps explain why marijuana users tend to see patterns in events that are not real, such as conspiracies [45] (Table 1).

In a study analyzing a college population, heavy users of marijuana displayed significantly greater impairment than light users on intentional/executive functions. This led to the conclusion that heavy marijuana use is associated with residual neuropsychological effects even after a day of supervised abstinence from the drug [46,47].

### What did the cases have in common?

| Cases of Marijuana Use and Symptoms | |
|---|---|
| **Case** | **Symptoms** |
| Michael Brown | Aggressiveness, Personality Change, Paranoia |
| Trayvon Martin | Aggressiveness, Personality Change, Paranoia |
| Laquan McDonald | Aggressiveness, Personality Change |
| Devon Guilford | Aggressiveness, Personality Change |
| Freddie Gray | Paranoia |
| Lakeisha Holloway | Aggressiveness, Personality Change |
| Robert Lewis Dear | Psychosis |
| Joseph Jesse Aldridge | Psychosis |
| Gerard Lee Loughner | Aggressiveness, Personality Change, Psychosis |
| Tsarnaev Brothers | Aggressiveness, Personality Change |
| Khalil Abu-Rayyam | Psychosis |

| | |
|---|---|
| Osam bin Laden | Paranoia, Psychosis |

**Table 1:** Marijuana uses and symptoms.

## Discussion

We apply the results of the research regarding the role of marijuana in violence. We use concepts such as personality changes, perpetrator violence, and psychosis to establish our association of marijuana with the unfortunate cases. The purpose is to illustrate negative but preventable tragic outcomes due to marijuana and its role in violence. The overall objective is to identify the role of marijuana and to suggest it is avoidable and causal nature in inducing violence [48-50].

In all the cases selected, marijuana use was present. For some of the individuals, marijuana use was confirmed by a physical test. In other cases, marijuana was present on their person, indentifying drug use. Moreover, some individuals of the case were identified as marijuana users by outside sources.

### Personality change toward aggression or violence (Chart 1)

| Paranoid Personality Disorder |
|---|
| A. A pervasive distrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following: |
| Suspects, without sufficient bases, those others are exploiting, harming, or deceiving him or her. |
| Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates. |
| Is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her. |
| Reads hidden demeaning or threatening meanings into benign remarks or events. |
| Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights). |
| Perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack. |
| Have recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner. |

**Chart 1:** Paranoid personality disorder (PPD) symptoms.

Present in all the cases, as a result of marijuana use, was the change in personality, aggressive behavior, paranoia and/or psychosis. All these symptoms have been documented by scientific research to be the result of marijuana use and intoxication. Another symptom, victimization, has a positive correlation with cannabis use, and the cases illustrate marijuana users and victimization [51,52]. In other words, marijuana users become victims of aggression in response to their perpetration under the influence of marijuana.

DSM V provides diagnostic categories for paranoid personality, paranoia and psychosis associated with marijuana use [53].

Michael Brown was a marijuana user and it was found in his system at the time of death. Further, Brown illustrated aggressive tendencies and victimization, as he was reported to aggressively assault a store clerk prior to his aggression towards a police officer. These actions were contrary to non-aggressive tendencies purported by those closest to Brown. Brown's intoxication of marijuana likely accounted for the aggression and assaults. While contributing factors such as race and poor police practices may have contributed to Brown's unfortunate death, Brown likely would have been alive had he not been a user of marijuana in this particular instance. Apparently he was acting under the influence in an uncharacteristically high risk manner.

Similar to Brown, Trayvon Martin was known to have used marijuana. He was suspended from school for marijuana use at the time of his altercation with Zimmerman. Under the influence of marijuana, Martin likely illustrated victim perpetration from marijuana which increased aggressive behavior through participation in the altercation with Zimmerman. This physical fight with Zimmerman was behavior is to the surprise of others who claimed Martin was mild mannered who likely would avoid such a confrontaion. Marijuana use likely created the fear and aggressive behavior due to poor judgment and threatening perceptions induced by marijuana, contribution to Martin's death [19,23].

Tamerlan Tsarnaev follows similar patterns. He was a known heavy marijuana user. There was a sharp change in his personality confirmed by his wife associated with very heavy use and involvement with marijuana, resulting in the violence towards his wife according to her. Likely, intoxication from marijuana created and contributed to the paranoid thoughts and poor judgment to detonate a bomb in a crowd of people [34,40].

Similarly, Laquan McDonald was a known marijuana user since 10 or 11 years old. The intoxication from the use of marijuana likely caused McDonald to slash a cop car's tire, as he was known to be respectful and reserved. His life would have been saved without marijuana induced aggressiveness and poor judgments, and senseless, high risk actions towards police [19,23].

Deven Guilford is another preventable but clear example high risk and poor judgement from marijuana use. After being stopped in his car, Guilford assaulted a police officer for unknown reasons and apparently paranoid reactions to police actions. Guilford was preoccupied with and user of marijuana at a relatively young age. His marijuana use likely contributed to the change in his personality to be aggressive and assaultive to provoke his death in a high risk police stop [19,23].

Similarly, Jared Lee Loughner was known to be a heavy marijuana user. People described a large personality change from his youth. Loughner went on a shooting spree, killing six people. Marijuana was likely a major contributor to the drastic change in personality toward violence. Had marijuana been identified as a problem, his aggressive and assaultive act may have been prevented and lives could have been saved [19,23].

Lakeisha Holloway shows another example of senseless loss. In contrast to her personality from her youth, she drove a car onto the sidewalk of the Las Vegas strip, killing one person and injuring others. Marijuana was in her system at the time of the attack and likely contributed to the lethal aggression exhibited, and likely, psychotic, paranoid thinking.

## Psychosis (Chart 2)

| Substance-Induced Psychotic Disorder |
|---|
| A. Presence of one or both of the following symptoms: |
| Delusions |
| Hallucinations |
| B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2): |
| The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication. |
| The involved substance is capable of producing the symptoms in Criterion A. |
| C. The disturbance is not better explained by a psychotic disorder that is not substance-induced. Such evidence of an independent psychotic disorder could include the following: |
| The symptoms preceded the onset of the substance use; the symptoms persist for a substantial period of time (e.g. about 1 month) after the cessation of acute withdrawal or sever intoxication; or there is other evidence of an independent non-substance-induced psychotic disorder (e.g. a history of recurrent non-substance-related episodes). |
| D. The disturbance does not occur exclusively during the course of a delirium. |
| E. The disturbance causes clinically significant distress or impairment in social, occupational or other |

**Chart 2:** Substance-induced psychotic disorder symptoms.

Studies have illustrated the connection between cannabis use and psychosis [54]. Marijuana has been shown to increase the risk for psychotic disorders and/or exacerbate pre-existing psychotic diseases. Consistent with research, marijuana resulting in psychosis is illustrated in many of the cases described above. Joseph Jesse Aldridge, described as a recluse, went on a shooting rampage after finding his mother deceased. Aldridge was a known marijuana user and had history of psychosis. His marijuana use likely contributed to his psychosis, and a major factor for the shooting rampage [55,56].

Similar to Aldridge, Jared Lee Loughner was admittedly a marijuana user. He suffered from a mental illness of paranoid schizophrenia. Loughner then went on a shooting spree killing six people. His marijuana use likely exacerbated the psychosis, which was a high risk factor for the shootings [33,35,55].

Analogous to Aldridge and Loughner, Robert Lewis Dear went on a shooting spree in Colorado. Dear moved to Colorado for easier access to marijuana. Dear also exhibited signs of mental health illness, psychosis and paranoia, which caused or exacerbated by marijuana, which resulted in his shooting spree [18,31].

While Khalil Abu-Rayyan did not result in a shooting rampage, this case illustrates the same ideas as previous cases. Abu-Rayyan used marijuana. He illustrated signs of psychosis through the threats of terrorism and martyrdom. Abu-Rayyan obtained the instruments to carry out his plans. The psychosis, contributing to the terroristic thoughts, marijuana use contributed to and exacerbated his aggressive behaviour [31,36,55].

Similar to Abu-Rayyan, Osama bin Laden also had notorious terroristic and paranoid behavior. Bin Laden was a marijuana user, growing high strength plants within his compound in Pakistan. Unfortunately, bin Laden's psychosis, associated and exacerbated by marijuana use, may have prompted him to carry out the most heinous terrorist attacks in history. Without marijuana use and subsequent psychosis, many deaths may not have occurred [31,55,56].

## Paranoia (Chart 3)

| Subtypes Delusional Disorder |
|---|
| **Grandiose type:** This subtype applies when the central theme of the delusion is the conviction of having some great (but unrecognized) talent or insight or having made some important discovery. |
| **Persecutory type:** This subtype applies when the central theme of the delusion involves the individual's belief that he or she is being conspired against, cheated, spied on, followed, poisoned or drugged, maliciously maligned, harassed or obstructed in the pursuit of long-term goals. |

**Chart 3:** Types of delusional disorder (DD).

In addition to psychosis and aggression, paranoia has been connected to marijuana intoxication [57,58]. Studies have illustrated THC significantly increase paranoia through a physical pathway. The cases described above illustrate such paranoia in marijuana users. For instance, Freddie Gray was arrested after he fled on the mere sight of police officers. During his arrest in the intoxicated state, he was injured which resulted in his death. Gray was a known drug addict and user of marijuana. His marijuana use likely induced paranoia thinking and poor judgment which prompted him to flee from police, threatening to him. Without marijuana and other drug intoxication, his cooperation likely would have been different, and he would avoided his high risk apprehension, and death avoided [34,36,40].

Similarly, Trayvon Martin got into an altercation with a Neighborhood Watch guard. Martin, speaking to his girlfriend, stated that a "creepy" man was following him and that he tried to evade the follower. His description is characteristic of apprehensive beliefs, and a sign of paranoia thought. Otherwise, Martin according to his family would not have fought with Zimmerman, had masituation escalated due to the paranoia, caused by the use of marijuana [34,36,40].

Osama bin Laden also illustrated paranoia, in letters that were discovered after his death. Paranoia was caused by his frequent marijuana use. This paranoia resulted in his adverse view of the US government. Unfavorable views toward the US resulting from extreme paranoia, coupled with psychosis, resulted in his terrorist attacks. Marijuana abstinence could have prevented the death of thousands of people [34,36,40].

These cases contained diverse variables: encounters with police, race, altercations, confrontation and mental illness. Other drug use was present but not the same across all cases. However, marijuana and violence are the common denominators in all the cases. Many were not victims of police aggression, some perpetuated police responses, some not. Diverse races and cultures were represented, and no stereotype was evident among the cases of violence and marijuana use. The variables, marijuana and violence were present in all cases.

An extensive review of the scientific literature document a clear association between marijuana and violence, psychosis, personality changes, poor judgment, aggression, victim perpetration. There are other possibilities and contributing factors in the execution of the violent behaviors, though probably not present in all cases. The purpose of this case report is to illustrate the probable role of marijuana in violent behaviors.

The review does not prove a causal relationship between marijuana and violence in these cases. Rather it establishes a highly documented association between marijuana and violence. A legal standard used for causation can be applied to illustrate this association. A legal cause is "but for" the actions or circumstances, the result would not have occurred. A proximate cause is the result was "foreseeable" based on the facts and actions. The most likely legal and proximate cause of violence in these cases was the use and intoxication from marijuana. No other variables fulfill these requirements.

## Conclusion

According to research studies, marijuana use causes aggressive behavior, causes or exacerbates psychosis and produce paranoias. These effects have been illustrated through case studies of highly publicized incidents and heightened political profiles.

These cases contain examples of repeated illustrations of aggression, psychosis and paranoia by marijuana users and intoxication. Ultimately, without the use and intoxication of marijuana, the poor judgment and misperceptions displayed by these individuals would not have been present, reducing the risk for actions that result in senseless deaths.

Import to these assertions, is that the current marijuana is far more potent in THC concentrations, the psychoactive component. Accordingly, and demonstrated in direct studies, more potent marijuana results in a greater risk for paranoid thinking and psychosis. In turn, paranoid behavior increases the risk for paranoid behaviors and predictably associated with aggressive and violent behaviors.

Marijuana use causes violent behavior through increased aggressiveness, paranoia and personality changes (more suspicious, aggressive and anger).

Recent illicit and "medical marijuana" (especially grown by care givers for medical marijuana) is of much high potency and more likely to cause violent behavior.

Marijuana use and its adverse effects should be considered in cases of acts of violence as its role is properly assigned to its high association.

Recognize that high potency marijuana is a predictable and preventable cause of tragic violent consequences.

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CONSTRUCTIONDIVE

DEEP DIVE

# High stakes: State cannabis laws make contractors' obligations hazy

As medical and recreational use of marijuana becomes more acceptable — and in some instances, legal — contractors are faced with a growing pool of candidates that are testing positive.

By Kim Slowey

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Many states in the U.S. have loosened up their regulation and restriction laws related to cannabis, or marijuana, in recent years, with 33 states and Washington, D.C., currently allowing it for medical reasons. Ten of those states and D.C. allow adult recreational use.

For employers, including those in the construction industry, this new status of marijuana, which used to be an illegal substance everywhere and under all circumstances in the U.S., presents some challenges — not the least of which is finding workers who can pass a hiring or post-accident/incident drug test.

"It's kind of the Wild West," said Tom Cecich, president of safety, health and environmental management consulting firm TFC & Associates and advisor to risk management firm Avetta. "You've got state laws that decriminalize the use of marijuana specifically, but, obviously, you have a federal law that can't be violated."

The federal government classifies cannabis as a Schedule I drug under the Controlled Substances Act, which means the government considers it to have no accepted medical use and carries with it a high chance of user abuse. Physicians aren't allowed to prescribe Schedule I drugs, so one can see how the federal law is in conflict with those regulating and advocating for medical marijuana.

In fact, last year, the Drug Enforcement Administration moved cannabis-containing substances with up to 0.1% tetrahydrocannabinol (THC) — the psychoactive component — that have also been approved by the Federal Drug Administration from Schedule I to Schedule V. The impetus was an anticonvulsant drug called Epidiolex, which contains a cannabis extract called cannabidiol (CBD). If the DEA had not made an allowance for certain cannabinoids, doctors would not have been able to prescribe them, even though they had FDA approval.

In their attempts not to run afoul of the federal requirements regarding cannabis, and to align themselves with the wishes of their clients, Cecich said most large construction companies

have decided that a positive drug test is a reason not to hire or, under some conditions like an accident, a reason to terminate, especially if the job in question is a safety-sensitive one.

Even where it's legal.

Unlike alcohol, there is no standard to detect and measure cannabis impairment, only a test that detects use. While psychoactive effects usually last a relatively short period of time, the rate at which cannabis leaves the system varies — in some cases, taking weeks. Also, cannabinoids can be stored in body fat, so the heavier someone is, the longer it can take to clear the body.

"Good employers who want to do the right thing are really being challenged," Cecich said.

And make no mistake, the contradiction between federal law and state law — exacerbated because there is no way to test for impairment — is taking its toll on the construction industry, which is suffering from a lack of skilled trade workers and many other positions like estimators and superintendents.

Labor conditions are tight in most parts of the country, said Brian Turmail of the Associated General Contractors of America, and adding to that problem is the fact that much of the industry has a zero-tolerance drug-use policy. Most companies don't want to be in the business of deciding how their employees spend their time off work, he said, but they have a legal obligation to make

sure their workers are sober when on the job — especially if that's a jobsite with heavy equipment and various hazards.

In Colorado, Cecich said, there's anecdotal evidence that as many as 15% or 20% of applicants test positive for a history of cannabis use.

Adding to the confusion are conflicting state hiring laws, making it almost impossible for multistate contractors to have one drug testing policy across their entire operation.

For example, in Maine, said attorney Benton Bodamer of Dickinson Wright in Columbus, Ohio, employers were initially not allowed to discriminate against their employees or new hires for off-duty consumption. Employers could generally only take action if they could prove the employee in question consumed marijuana on the job, although, he added, more recent updates have softened and confused that black line.

In Colorado, said Turmail, a state with some of the most liberal use laws, courts have upheld an employer's right to zero-tolerance policies — even when it comes to medical marijuana — and to terminate even if there is no evidence of impairment.

Some state courts, said attorney Wendy Lane of Greenberg Glusker Fields Claman & Machtinger LLP in Los Angeles, have started looking at medical marijuana accommodations that employers could make before terminating, possibly providing a solution for contractors who are interested in a middle ground.

In Massachusetts, she said, a court held that an employer has an obligation to determine whether an employee using medical marijuana is impaired and to evaluate potential accommodations involving scheduling and nature of duties and to look at how safety-sensitive the job is before termination.

“The court said, unless you engage in an interactive process,” said Lane, “how can you assess whether you’re reasonably accommodating this person?”

Insurance costs also come into play. Insurance carriers will likely charge more for general liability, workers’ compensation or other forms of business insurance if an employer chooses not to perform pre-employment drug testing, but contractors have to weigh how much a higher premium would cost versus not being able to have enough labor to bid on and plan for new work.

Employees also need to keep in mind that they can be denied all or a portion of workers’ compensation benefits in many states if they test positive for marijuana after an accident. Even in Colorado, workers can lose 50% of their benefits if they were impaired at the time of the accident. But with no sure test for impairment, employees are taking a chance that a decision on benefits will not go in their favor.

**Where does all this leave contractors?**

First, using cannabis on the job will always be a no-no in the construction industry and most likely a fireable offense. Second,

contractors working on federal projects have no option but to maintain a drug-free workplace.

For everyone else, Bodamer said there are several things that need to happen to end the confusion about marijuana consumption on the part of both employers and employees, and perhaps find a solution for those testing positive but who are not "high" on the job:

1. Employers should be thoughtful about their drug testing policies, develop coherent approaches and understand the repercussions. They need to be aware if and how their policies will exclude future candidates or affect current employees.
2. There needs to be clarity on how to differentiate between who is impaired and who is not, with special attention to those who test positive because of participation in a state-compliant medical program.
3. There also needs to be clarity between state and federal law, which could would happen with ppassage of the STATES (Strengthening the Tenth Amendment Through Entrusting States) Act, a bipartisan bill that would amend the Controlled Substances Act to allow states to establish their own marijuana laws, which would be exempt from federal enforcement.

Turmail said the AGC has been exploring and monitoring the issue and that the key might be in developing a scientifically reliable impairment test. With such an advancement, he said,

insurance companies are more likely to evolve and test for impairment, not just use.

As a side note, there is also some evidence, Turmail said, that medical marijuana can help relieve the chronic pain that plagues many construction workers and possibly assist with potential opioid dependency issues.

In order to be able to compete, Cecich said, some contractors have chosen to forego testing or allow someone who tests positive to fill a non-safety-sensitive position. This could include estimators or someone in the accounting department but would most likely be an option only for smaller companies and those with less risky scopes of work.

For safety-sensitive positions like crane operators, however, not much is going to change.

If a client asked Lane if it could overlook a positive test for someone applying to operate dangerous machinery like a crane or other heavy equipment, she said she might initiate a discussion about engaging in the interactive process with that person to determine how he or she could fill some role but would be reluctant to advise the company employ someone who tests positive for that position.

“It’s not smart to take on that liability,” she said.

However, if individuals are motivated and really want the job, she said, employers might think about giving them another

opportunity if the previous use was recreational.

“They could say, ‘Let it clear the system,” Lane said, “ ‘and we’ll give you a second chance.’ ”

# Marijuana, Mental Illness, and Violence

imprimis.hillsdale.edu/marijuana-mental-illness-violence/

**Alex Berenson**
Author, *Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence*

**Alex Berenson** is a graduate of Yale University with degrees in history and economics. He began his career in journalism in 1994 as a business reporter for the *Denver Post*, joined the financial news website TheStreet.com in 1996, and worked as an investigative reporter for *The New York Times* from 1999 to 2010, during which time he also served two stints as an Iraq War correspondent. In 2006 he published *The Faithful Spy*, which won the 2007 Edgar Award for best first novel from the Mystery Writers of America. He has published ten additional novels and two nonfiction books, *The Number: How the Drive for Quarterly Earnings Corrupted Wall Street and Corporate America* and *Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence.*

*The following is adapted from a speech delivered on January 15, 2019, at Hillsdale College's Allan P. Kirby, Jr. Center for Constitutional Studies and Citizenship in Washington, D.C.*

Seventy miles northwest of New York City is a hospital that looks like a prison, its drab brick buildings wrapped in layers of fencing and barbed wire. This grim facility is called the Mid-Hudson Forensic Psychiatric Institute. It's one of three places the state of New York sends the criminally mentally ill—defendants judged not guilty by reason of insanity.

Until recently, my wife Jackie—Dr. Jacqueline Berenson—was a senior psychiatrist there. Many of Mid-Hudson's 300 patients are killers and arsonists. At least one is a cannibal. Most have been diagnosed with psychotic disorders like schizophrenia that provoked them to violence against family members or strangers.

A couple of years ago, Jackie was telling me about a patient. In passing, she said something like, *Of course he'd been smoking pot his whole life.*

Of course? I said.

*Yes, they all smoke.*

So marijuana causes schizophrenia?

I was surprised, to say the least. I tended to be a libertarian on drugs. Years before, I'd covered the pharmaceutical industry for *The New York Times*. I was aware of the claims about marijuana as medicine, and I'd watched the slow spread of legalized cannabis without much interest.

Jackie would have been within her rights to say, *I know what I'm talking about, unlike you.* Instead she offered something neutral like, *I think that's what the big studies say. You should read them.*

So I did. The big studies, the little ones, and all the rest. I read everything I could find. I talked to every psychiatrist and brain scientist who would talk to me. And I soon realized that in all my years as a journalist I had never seen a story where the gap between insider and outsider knowledge was so great, or the stakes so high.

I began to wonder why—with the stocks of cannabis companies soaring and politicians promoting legalization as a low-risk way to raise tax revenue and reduce crime—I had never heard the truth about marijuana, mental illness, and violence.

***

Over the last 30 years, psychiatrists and epidemiologists have turned speculation about marijuana's dangers into science. Yet over the same period, a shrewd and expensive lobbying campaign has pushed public attitudes about marijuana the other way. And the effects are now becoming apparent.

Almost everything you think you know about the health effects of cannabis, almost everything advocates and the media have told you for a generation, is wrong.

They've told you marijuana has many different medical uses. In reality marijuana and THC, its active ingredient, have been shown to work only in a few narrow conditions. They are most commonly prescribed for pain relief. But they are rarely tested against other pain relief drugs like ibuprofen—and in July, a large four-year study of patients with chronic pain in Australia showed cannabis use was associated with *greater* pain over time.

They've told you cannabis can stem opioid use—"Two new studies show how marijuana can help fight the opioid epidemic," according to Wonkblog, a *Washington Post* website, in April 2018— and that marijuana's effects as a painkiller make it a potential substitute for opiates. In reality, like alcohol, marijuana is too weak as a painkiller to work for most people who truly *need* opiates, such as terminal cancer patients. Even cannabis advocates, like Rob Kampia, the co-founder of the Marijuana Policy Project, acknowledge that they have always viewed medical marijuana laws primarily as a way to protect recreational users.

As for the marijuana-reduces-opiate-use theory, it is based largely on a single paper comparing overdose deaths by state before 2010 to the spread of medical marijuana laws— and the paper's finding is probably a result of simple geographic coincidence. The opiate epidemic began in Appalachia, while the first states to legalize medical marijuana were in the West. Since

2010, as both the epidemic and medical marijuana laws have spread nationally, the finding has vanished. And the United States, the Western country with the most cannabis use, also has by far the worst problem with opioids.

Research on individual users—a better way to trace cause and effect than looking at aggregate state-level data—consistently shows that marijuana use leads to other drug use. For example, a January 2018 paper in the *American Journal of Psychiatry* showed that people who used cannabis in 2001 were almost three times as likely to use opiates three years later, even after adjusting for other potential risks.

Most of all, advocates have told you that marijuana is not just safe for people with psychiatric problems like depression, but that it is a potential treatment for those patients. On its website, the cannabis delivery service Eaze offers the "Best Marijuana Strains and Products for Treating Anxiety." "How Does Cannabis Help Depression?" is the topic of an article on Leafly, the largest cannabis website. But a mountain of peer-reviewed research in top medical journals shows that marijuana can cause or worsen severe mental illness, especially psychosis, the medical term for a break from reality. Teenagers who smoke marijuana regularly are about three times as likely to develop schizophrenia, the most devastating psychotic disorder.

After an exhaustive review, the National Academy of Medicine found in 2017 that "cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk." Also that "regular cannabis use is likely to increase the risk for developing social anxiety disorder."

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Over the past decade, as legalization has spread, patterns of marijuana use—and the drug itself—have changed in dangerous ways.

Legalization has not led to a huge increase in people using the drug casually. About 15 percent of Americans used cannabis at least once in 2017, up from ten percent in 2006, according to a large federal study called the National Survey on Drug Use and Health. (By contrast, about 65 percent of Americans had a drink in the last year.) But the number of Americans who use cannabis *heavily* is soaring. In 2006, about three million Americans reported using cannabis at least 300 times a year, the standard for daily use. By 2017, that number had nearly tripled, to eight million, approaching the twelve million Americans who drank alcohol every day. Put another way, one in 15 drinkers consumed alcohol daily; about one in five marijuana users used cannabis that often.

Cannabis users today are also consuming a drug that is far more potent than ever before, as measured by the amount of THC—delta-9-tetrahydrocannabinol, the chemical in cannabis responsible for its psychoactive effects—it contains. In the 1970s, the last time this many Americans used cannabis, most marijuana contained less than two percent THC. Today, marijuana routinely contains 20 to 25 percent THC, thanks to sophisticated farming and cloning techniques—as well as to a demand by users for cannabis that produces a stronger high more

quickly. In states where cannabis is legal, many users prefer extracts that are nearly pure THC. Think of the difference between near-beer and a martini, or even grain alcohol, to understand the difference.

These new patterns of use have caused problems with the drug to soar. In 2014, people who had diagnosable cannabis use disorder, the medical term for marijuana abuse or addiction, made up about 1.5 percent of Americans. But they accounted for eleven percent of all the psychosis cases in emergency rooms—90,000 cases, 250 a day, triple the number in 2006. In states like Colorado, emergency room physicians have become experts on dealing with cannabis-induced psychosis.

Cannabis advocates often argue that the drug can't be as neurotoxic as studies suggest, because otherwise Western countries would have seen population-wide increases in psychosis alongside rising use. In reality, accurately tracking psychosis cases is impossible in the United States. The government carefully tracks diseases like cancer with central registries, but no such registry exists for schizophrenia or other severe mental illnesses.

On the other hand, research from Finland and Denmark, two countries that track mental illness more comprehensively, shows a significant increase in psychosis since 2000, following an increase in cannabis use. And in September of last year, a large federal survey found a rise in serious mental illness in the United States as well, especially among young adults, the heaviest users of cannabis.

According to this latter study, 7.5 percent of adults age 18-25 met the criteria for serious mental illness in 2017, double the rate in 2008. What's especially striking is that adolescents age 12-17 don't show these increases in cannabis use and severe mental illness.

A caveat: this federal survey doesn't count individual cases, and it lumps psychosis with other severe mental illness. So it isn't as accurate as the Finnish or Danish studies. Nor do any of these studies *prove* that rising cannabis use has caused population-wide increases in psychosis or other mental illness. The most that can be said is that they offer intriguing evidence of a link.

Advocates for people with mental illness do not like discussing the link between schizophrenia and crime. They fear it will stigmatize people with the disease. "Most people with mental illness are not violent," the National Alliance on Mental Illness (NAMI) explains on its website. But wishing away the link can't make it disappear. In truth, psychosis is a shockingly high risk factor for violence. The best analysis came in a 2009 paper in *PLOS Medicine* by Dr. Seena Fazel, an Oxford University psychiatrist and epidemiologist. Drawing on earlier studies, the paper found that people with schizophrenia are five times as likely to commit violent crimes as healthy people, and almost 20 times as likely to commit homicide.

NAMI's statement that most people with mental illness are not violent is of course accurate, given that "most" simply means "more than half"; but it is deeply misleading. Schizophrenia is rare. But people with the disorder commit an appreciable fraction of all murders, in the range of six to nine percent.

"The best way to deal with the stigma is to reduce the violence," says Dr. Sheilagh Hodgins, a professor at the University of Montreal who has studied mental illness and violence for more than 30 years.

The marijuana-psychosis-violence connection is even stronger than those figures suggest. People with schizophrenia are only moderately more likely to become violent than healthy people when they are taking antipsychotic medicine and avoiding recreational drugs. But when they use drugs, their risk of violence skyrockets. "You don't just have an increased risk of one thing—these things occur in clusters," Dr. Fazel told me.

Along with alcohol, the drug that psychotic patients use more than any other is cannabis: a 2010 review of earlier studies in *Schizophrenia Bulletin* found that 27 percent of people with schizophrenia had been diagnosed with cannabis use disorder in their lives. And unfortunately—despite its reputation for making users relaxed and calm—cannabis appears to provoke many of them to violence.

A Swiss study of 265 psychotic patients published in *Frontiers of Forensic Psychiatry* last June found that over a three-year period, young men with psychosis who used cannabis had a 50 percent chance of becoming violent. That risk was four times higher than for those with psychosis who didn't use, even after adjusting for factors such as alcohol use. Other researchers have produced similar findings. A 2013 paper in an Italian psychiatric journal examined almost 1,600 psychiatric patients in southern Italy and found that cannabis use was associated with a ten-fold increase in violence.

The most obvious way that cannabis fuels violence in psychotic people is through its tendency to cause paranoia—something even cannabis advocates acknowledge the drug can cause. The risk is so obvious that users joke about it and dispensaries advertise certain strains as less likely to induce paranoia. And for people with psychotic disorders, paranoia can fuel extreme violence. A 2007 paper in the *Medical Journal of Australia* on 88 defendants who had committed homicide during psychotic episodes found that most believed they were in danger from the victim, and almost two-thirds reported misusing cannabis—more than alcohol and amphetamines combined.

Yet the link between marijuana and violence doesn't appear limited to people with preexisting psychosis. Researchers have studied alcohol and violence for generations, proving that alcohol is a risk factor for domestic abuse, assault, and even murder. Far less work has been done on marijuana, in part because advocates have stigmatized anyone who raises the issue. But studies showing that marijuana use is a significant risk factor for violence have quietly piled up. Many of them weren't even designed to catch the link, but they did. Dozens of such studies exist, covering everything from bullying by high school students to fighting among vacationers in Spain.

In most cases, studies find that the risk is at least as significant as with alcohol. A 2012 paper in the *Journal of Interpersonal Violence* examined a federal survey of more than 9,000 adolescents and found that marijuana use was associated with a doubling of domestic violence; a 2017

paper in *Social Psychiatry and Psychiatric Epidemiology* examined drivers of violence among 6,000 British and Chinese men and found that drug use—the drug nearly always being cannabis—translated into a five-fold increase in violence.

Today that risk is translating into real-world impacts. Before states legalized recreational cannabis, advocates said that legalization would let police focus on hardened criminals rather than marijuana smokers and thus reduce violent crime. Some advocates go so far as to claim that legalization *has* reduced violent crime. In a 2017 speech calling for federal legalization, U.S. Senator Cory Booker said that "states [that have legalized marijuana] are seeing decreases in violent crime." He was wrong.

The first four states to legalize marijuana for recreational use were Colorado and Washington in 2014 and Alaska and Oregon in 2015. Combined, those four states had about 450 murders and 30,300 aggravated assaults in 2013. Last year, they had almost 620 murders and 38,000 aggravated assaults—an increase of 37 percent for murders and 25 percent for aggravated assaults, far greater than the national increase, even after accounting for differences in population growth.

Knowing exactly how much of the increase is related to cannabis is impossible without researching every crime. But police reports, news stories, and arrest warrants suggest a close link in many cases. For example, last September, police in Longmont, Colorado, arrested Daniel Lopez for stabbing his brother Thomas to death as a neighbor watched. Daniel Lopez had been diagnosed with schizophrenia and was "self-medicating" with marijuana, according to an arrest affidavit.

In every state, not just those where marijuana is legal, cases like Lopez's are far more common than either cannabis or mental illness advocates acknowledge. Cannabis is also associated with a disturbing number of child deaths from abuse and neglect—many more than alcohol, and more than cocaine, methamphetamines, and opioids combined—according to reports from Texas, one of the few states to provide detailed information on drug use by perpetrators.

These crimes rarely receive more than local attention. Psychosis-induced violence takes particularly ugly forms and is frequently directed at helpless family members. The elite national media prefers to ignore the crimes as tabloid fodder. Even police departments, which see this violence up close, have been slow to recognize the trend, in part because the epidemic of opioid overdose deaths has overwhelmed them.

So the black tide of psychosis and the red tide of violence are rising steadily, almost unnoticed, on a slow green wave.

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For centuries, people worldwide have understood that cannabis causes mental illness and violence—just as they've known that opiates cause addiction and overdose. Hard data on the relationship between marijuana and madness dates back 150 years, to British asylum registers in India. Yet 20 years ago, the United States moved to encourage wider use of cannabis and opiates.

In both cases, we decided we could outsmart these drugs—that we could have their benefits without their costs. And in both cases we were wrong. Opiates are riskier, and the overdose deaths they cause a more imminent crisis, so we have focused on those. But soon enough the mental illness and violence that follow cannabis use will also be too widespread to ignore.

Whether to use cannabis, or any drug, is a personal decision. Whether cannabis should be legal is a political issue. But its precise legal status is far less important than making sure that anyone who uses it is aware of its risks. Most cigarette smokers don't die of lung cancer. But we have made it widely known that cigarettes cause cancer, full stop. Most people who drink and drive don't have fatal accidents. But we have highlighted the cases of those who do.

We need equally unambiguous and well-funded advertising campaigns on the risks of cannabis. Instead, we are now in the worst of all worlds. Marijuana is legal in some states, illegal in others, dangerously potent, and sold without warnings everywhere.

But before we can do anything, we—especially cannabis advocates and those in the elite media who have for too long credulously accepted their claims—need to come to terms with the truth about the science on marijuana. That adjustment may be painful. But the alternative is far worse, as the patients at Mid-Hudson Forensic Psychiatric Institute—and their victims—know.