

The National Academies of Science, Engineering and Medicine Report

Researchers Evaluate Evidence on Cannabis as Medicine

By Fred Gardner

In January 2017 the National Academies of Science, Engineering and Medicine published a 468-page report, “The Health Effects of Cannabis and the Cannabinoids: The Current State of Evidence and Recommendations for Research.”

Founded as the National Academy of Sciences in 1863, the NAS provides expert advice to US government agencies. Academy members elect new members based on their research achievements.

The NAS Cannabis Report was based on papers published in peer-reviewed journals since 1999 (when a predecessor report was issued by the Institute of Medicine, a branch of the NAS). The editorial committee that compiled the Report explained their method.

“The committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO and initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by ‘anonymous’ authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.”

Levels of Evidence

The committee assessed the quality of the studies supporting each finding of therapeutic effect. They sorted them thus:

“CONCLUSIVE = strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.”

“SUBSTANTIAL = strong evidence to support the conclusion...”

“MODERATE = some evidence to support the conclusion...”

“LIMITED = weak evidence to support the conclusion...”

“No OR INSUFFICIENT = no or insufficient evidence to support the conclusion...”

Key findings follow:

Therapeutic Effects

“There is CONCLUSIVE OR SUBSTANTIAL evidence that cannabis or cannabinoids are effective:

- For the treatment for chronic pain in adults (cannabis).
- Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids).
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids).

“There is MODERATE evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols).

“There is LIMITED evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids).
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids).
- Improving symptoms of Tourette syndrome (THC capsules).
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol)
- Improving symptoms of post-traumatic stress disorder (nabilone; one single, small fair-quality trial).



MARIE MCCORMICK, MD, Chair, National Academy of Sciences’ Committee on the Health Effects of Marijuana, at the introductory press conference.

“There is LIMITED evidence of a statistical association between cannabinoids and:

- Better outcomes after a traumatic brain injury or intracranial hemorrhage

“There is LIMITED evidence that cannabis or cannabinoids are ineffective for:

- Improving symptoms associated with dementia (cannabinoids).
- Improving intraocular pressure associated with glaucoma (cannabinoids).
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone).

The benefits for which there is conclusive evidence are characterized as “modest” in the NAS Report. They might not seem “modest” to those in need of relief.

“In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.

“In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.

“In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.

“For these conditions, the effects of cannabinoids are MODEST; for all other conditions evaluated, there is inadequate information to assess their effects.

“There is NO OR INSUFFICIENT EVIDENCE to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids).
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids).
- Symptoms of irritable bowel syndrome (dronabinol).

- Epilepsy (cannabinoids)
- * *Publication of Epidiolex clinical trial results in the New England Journal of Medicine in May 2017 would provide conclusive evidence of benefit in the treatment of two severe forms of childhood epilepsy, by the NAS definition. Also, see story on page 29.*
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids).
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids).
- Chorea and certain neuropsychiatric symptoms associated with Huntington’s disease (oral cannabinoids).
- Motor system symptoms associated with Parkinson’s disease or the levodopa-induced dyskinesia (cannabinoids).
- Dystonia (nabilone and dronabinol).
- Achieving abstinence in the use of addictive substances (cannabinoids).
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol).”

‘Other Health Effects’ Assessed

Cancer

“There is MODERATE evidence of no statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking)
- Incidence of head and neck cancers.

I had to re-read this a few times. See box on page 28. —FG

“There is limited evidence of a statistical association between cannabis smoking and: Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking).

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

- Incidence of esophageal cancer (cannabis smoking)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi’s sarcoma, or bladder cancer.
- Subsequent risk of developing acute myeloid leukemia, acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use).

Cardiometabolic Risk

“There is limited evidence of a statistical association between cannabis smoking and the triggering of acute myocardial infarction.

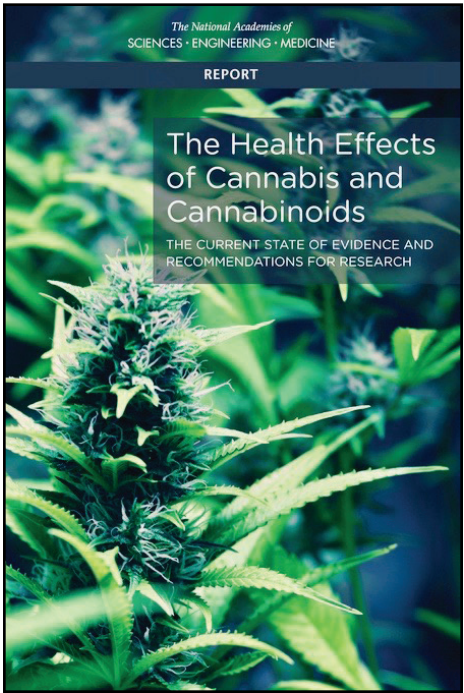
- Decreased risk of metabolic syndrome and diabetes but increased risk of prediabetes.

“There is no evidence to support or refute a statistical association between chronic effects of cannabis use and increased risk of acute myocardial infarction.”

Respiratory Disease

“Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.

“Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.



“It is unclear whether cannabis use is associated with COPD, asthma, or worsened lung function.

Injury and Death

“Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.

“In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.

“It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

Psychosocial

“Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.

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

- Impaired academic achievement and education outcomes
- Increased rates of unemployment and/or low income
- Impaired social functioning or engagement in developmentally appropriate social roles.

“There is limited evidence of a statistical association between *sustained abstinence* from cannabis use and impairments in the cognitive domains of learning, memory, and attention.” [Sic.]

Prenatal, perinatal and neonatal exposure

“Smoking cannabis during pregnancy is linked to lower birth weight.

[Disputed by Ko et al in Drug Alcohol Dependence 2018.]

Problem cannabis use

“Greater frequency of cannabis use increases the likelihood of developing Cannabis Use Disorder.

“Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

Mental Health

“Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk.

“In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.

“Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and post-traumatic stress disorder.

“For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.

Heavy cannabis users are more likely to report thoughts of suicide than non-users.

“Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

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Report Findings With the Strongest Research Evidence

- Initiating cannabis use at a young age is a risk factor for developing problematic cannabis use.
- Pregnant women who smoke increase the risk that their baby will be born with lower birth weight.
- Long-term cannabis smoking causes chronic breathing problems.
- Some people with chronic pain, muscle spasms from multiple sclerosis, or nausea and vomiting from cancer chemotherapy obtain some relief of their symptoms from using cannabis-based products or cannabis.
- Researchers who want to study the effects of cannabis face substantial obstacles.

SLIDE FROM NAS PRESS CONFERENCE emphasized risks of cannabis use. Benefits were fourth on list —“Some people” achieved “some relief.” A study by Ko et al in *Drug Alcohol Dependence 2018* would refute the supposedly strong association of cannabis use during pregnancy and lower birthweight.

Clinicians ignored from previous page

cal Use of Drugs:

“In the end, the decisions in this field are very complex moral decisions based on a number of imponderables and competing values, and in many cases they involve a choice of the lesser of evils. There are few easy choices. There is no way that these kind of decisions can be passed over to experts. In the end, they will have to be handed back to [the public].”

Tod Mikuriya’s study of the pre-prohibition medical literature led him to conclude that marijuana was useful in treating a wide range of conditions. In the early 1990s his interviews with members of the San Francisco Cannabis Buyers Club confirmed this insight. He inferred that compounds in cannabis were affecting almost every physiological function. He wrote numerous case reports showing that cannabis can be used as a “harm reduction” substitute for alcohol, opioids, and other drugs with serious adverse side-effects.

For a few years after cannabis was legalized for medical use in California, Mikuriya was the only doctor known to readily issue approvals for less-than-grave conditions such as chronic pain and depression. As other doctors began specializing in treating cannabis users, Mikuriya organized the California Cannabis Research Medical Group, which became the Society of Cannabis Clinicians (SCC) when doctors from other states began joining.

Mikuriya saw the need for a journal in which cannabis clinicians could share their findings and observations. I helped him launch *O’Shaughnessy’s* in 2003. We published a number of case reports, some brief and some detailed.

Mikuriya’s own paper “Cannabis as a First-Line Treatment for Childhood Mental Disorders” (*O’Shaughnessy’s* Spring 2006) is a single, detailed case report.

“Cannabis as a Substitute for Alcohol” is based on 92 case histories, ran in

Three doctors who respected clinical evidence



Geoffrey Guy, Raphael Mechoulam and Tod Mikuriya at the 1999 International Cannabinoid Research Society meeting in Acapulco. Guy’s GW Pharmaceuticals funded Notcutt’s study based on N-of-1 trials.

Photo by Fred Gardner



Tod Mikuriya’s case report on a 15-year old patient “who had been prescribed stimulants, antidepressants, analgesics, and antipsychotics that exacerbated his problems. Cannabis provided a benign, effective alternative.” The boy’s initial problem had been insomnia. Mikuriya generalized: “The first-line treatment for any condition, efficacy being equal, would be the drug or procedure least likely to cause harm. Given the benign side effect profile of cannabis, it should be the first line of treatment in a wide range of childhood mental disorders, including persistent insomnia.”



Ten years after California voters legalized cannabis for medical use, Mikuriya and colleagues in the Society of Cannabis Clinicians reported findings and observations in *O’Shaughnessy’s*. “A vast public-health experiment has been conducted in the nation’s most populous state. What have doctors learned about the medical efficacy and safety of cannabis?” The 2006 SCC survey documented patients reporting similar patterns of benefit (which may in time be confirmed by randomized placebo-controlled double-blinded clinical trials.)

O’Shaughnessy’s (Summer ‘03) and the *Journal of Cannabis Therapeutics*, 2004.) I doubt there will ever be a more insightful treatment of the subject.

In 2006, the 10-year point of legalization for medical use, Mikuriya surveyed his colleagues and published the results in a paper, “Medical Marijuana in California, 1996-2006” (*O’Shaughnessy’s*, Winter/Spring 2007).

All the SCC doctors reported in 2006 that pain patients were reducing opioid use —typically by 50%— by adding cannabis to their regimen.

noted in the SCC survey. To cite but one example, lowered resistance to graft implantation was reported in a case note by William Toy, MD:

“A 62-year-old man who had a heart transplant from the Stanford program 22 years ago. He apparently is the longest surviving transplant patient in the program. He has been using large doses of cannabis ever since he received the transplant. He is convinced that cannabis not only reduces the side-effects of his anti-rejection drugs, but that it has anti-rejection properties. He feels that he owes his star status in Dr. Shumway’s program to the modulation of his immune system by cannabis.”

The NAS decision to ignore cannabis clinicians’ case reports is blacklisting by algorithm. The findings of cannabis clinicians have been barred from “the literature.” Their “quality of evidence” is deemed inadequate. The word *published* simply does not apply to articles not indexed in PubMed Central.

The survey by Mikuriya et al may have been printed on electrobrite paper and distributed in 2007 (25,000 copies) by doctors and dispensary operators, but it was not “published.” Nor did you just read a citation to a case note by Dr. Toy, because only material published in “the literature” can be cited.

The language of Capital-S Science supersedes workaday English.

The clinical evidence —what patients reported to specialists monitoring their cannabis use— will undoubtedly be confirmed the federal stranglehold on research weakens in the years ahead.

All the SCC doctors reported in 2006 that pain patients were reducing opioid use —typically by 50%— by adding cannabis to their regimen. This is how Helen Nunberg, MD, worded it: “49% of patients using cannabis for chronic pain were previously prescribed an opioid (such as hydrocodone) by their personal physician.” Many of the SCC doctors’ patients had gotten off opioids entirely.

Unusual benefits of cannabis were also

NAS Report from page 26

Abuse of other substances

“Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

“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. 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.
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use).
- A small increased risk for the development of depressive disorders.
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users.
- Increased incidence of suicide completion.
- Increased incidence of social anxiety disorder (regular cannabis use)

“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.

“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.
- The likelihood of developing bipolar disorder, particularly among regular or daily users.
- The development of any type of anxiety disorder, except social anxiety disorder.
- Increased symptoms of anxiety (near daily cannabis use).
- Increased severity of post-traumatic stress disorder symptoms among individuals with post-traumatic stress disorder.

“There is NO EVIDENCE to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders.
- The development of post-traumatic stress disorder.

“Heavy cannabis users are more likely to report thoughts of suicide than non-users.

“Regular cannabis use is likely to increase the risk for developing social anxiety disorder.”

And that, to quote a phrase, is “what the Science tells us” —about the health effects of cannabis and the cannabinoids.

Cannabis and lung cancer: NIDA’s dream dies hard

The expression “moving the goalposts back” refers to a situation in which you perform all the required tasks, only to be told that more tasks are required. It came to mind when I read in the NAS Report: “There is moderate evidence of no statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking)
- Incidence of head and neck cancers.”

The findings announced by UCLA pulmonologist Donald Tashkin in 2005 were based on a clinical trial that was “gold standard” in every way. He intended the study to be definitive. There had been contradictory findings and he wanted to resolve the basic question: is there an association between marijuana use and lung cancer?

The study by Tashkin and colleagues from the UCLA School of Medicine was well funded by NIDA. The Los Angeles County Cancer Surveillance program provided the names of 1,209 L.A. residents aged 59 or younger with cancer (611 lung, 403 oral/pharyngeal, 90 laryngeal, 108 esophageal).

Interviewers collected extensive lifetime histories of marijuana, tobacco, alcohol and other drug use, and data on diet, occupational exposures, family history of cancer, and various “socio-demographic factors.”

Some 1100 controls were found based on age, gender and neighborhood. The researchers controlled for tobacco use and calculated the relative risk of marijuana use resulting in lung and upper airways cancers. Among marijuana-only users, Tashkin reported, “We found absolutely no suggestion of a dose response.”

Given the quality of Tashkin’s clinical trial, how did the NAS committee evaluating the link between cannabis and lung cancer decide that the evidence for “no association” was not conclusive, not substantial, but only “moderate?”

It turns out that the committee had been instructed not to consider individual studies, but to rely on the meta-analyses and systematic reviews published in the literature. Tashkin’s very clear findings had gotten blurred in the process —a meta-analysis had mushed it up with a Finnish study that didn’t control for alcohol use! A member of the committee reminds me not to be so negative: “‘Moderate evidence’ means there *is* evidence.””