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 "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, NASEM provides expert advice to US government agencies. Academy members elect new members based on their research achievements.

The NASEM Cannabis Report was based on papers published in peer-reviewed journals since 1999 (when a predecessor report was issued). As explained in the Report:

"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

After winnowing the grain from the rechaff, the committee assessed the quality of the evidence supporting each finding of therapeutic effect. There were five levels:

"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 = what it says.

Analogous rankings were given for other health effects of cannabis or cannabinoids. For example, "Limited evidence for other health effects [means] there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors."

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



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

viduals with social anxiety disorders (cannabidiol)

• Improving symptoms of post-traumatic stress disorder (nabilone; one single, small fair-quality trial).

"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 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 (cannabi-noids).

• Symptoms of irritable bowel syndrome (dronabinol).

• Epilepsy (cannabinoids)*

• 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 levodopainduced 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)."

* The categorization of Epilepsy is outdated. Publication of GW Pharmaceuticals' Epidiolex clinical trial results in the New England Journal of Medicine pro-

continued on next page

Input from clinicians systematically ignored

By Fred Gardner

The NASEM press release described the 468-page Report thus: "One of the most **comprehensive** studies of recent research... offers a **rigorous** review of relevant scientific research published since 1999... summarizes the current state of **evidence regarding what is known** about the health impacts of cannabis."

The 1999 reference is to a predecessor report by the Institute of Medicine (now a division of the NASEM). Like the IOM Report, the NASEM Report is being widely cited as authoritative. It could be subtitled, "The Truth According to Evidence-Based Medicine."

Seven authors of the report took part in a "Stakeholders Engagement Meeting" that was streamed live from NASEM headquarters in Washington, DC on February 21, 2017.

I was at my computer in Alameda, California, a minute or two before the event began, with an audio recorder handy in case it got interesting. McCormick said that to her knowledge the NAS search had not turned up any papers based on N-of-1 trials.

a moderator to a panel chaired by Harvard Medical School professor Marie McCormick, MD.

McCormick said that to her knowledge the NASEM reviewers had not come across any papers based on N-of-1 trials. "We were looking for peer-reviewed papers that were published. Most conferences are not peer-reviewed. Case reports basicallty are anecdotal evidence without adequate conrols so it's very difficult to interpret them. And I don't think we found any N-of1-studies. (*Turning to the other panelists*) Anyone? Any N-of-1 studies? I 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."

It makes sense to exclude editorials, commentaries and papers for which no one claims attribution, but why ignore findings reported at scientific conferences? The International Cannabinoid Research Society subjects all proposals for presentations at their annual symposium to a peer-review process. It was at the 2005 ICRS meeting that UCLA pulmonologist Donald Tashkin reported the results of his monumental study showing that cannabis smoking does not cause lung cancer, and might even exert a protective effect.

O'Shaughnessy's reported Tashkin's continued on next page

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 indiThe screen was inviting viewers to submit questions, so I typed in, "How much weight did the investigators give to case reports, conference abstracts, and N-of-1 studies?" (Three approaches by which cannabis clinicians have documented their findings.)

As soon as the videocast began, to my surprise, my question was read aloud by

Anaesthesia, 2004, 59, pages 440-452

Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies

William Notcutt,¹ Mario Price,² Roy Miller,³ Samantha Newport,⁴ Cheryl Phillips,⁴ Susan Simmons⁵ and Cathy Sansom⁵

1 Consultant Anaesthetist, 2 Senior Pharmacist, 3 Specialist Registrar, Anaesthesia, 4 Research Assistant, 5 Registered Nurse, Department of Anaesthesia, James Paget Hospital, Louvestoff Road, Great Yarmouth Norfolk NR 31 6LA UK

don't think we saw any —that were pub lished, in any case.

The NASEM report provides this account of how it was produced:

"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



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NASEM Report from previous page

vides conclusive evidence of benefit in the treatment of two severe forms of childhood epilepsy, by NASEM's definition.

'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.

"There is limited evidence of a staistical 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

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 NASEM PRESS CONFERENCE emphasized risks of cannabis use. Benefits were fourth on list -- "Some people" achieved "some relief." A recent study refuted the supposedly strong association of cannabis use during pregnancyand lower birthweight.

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.

Immunity

"There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.

"There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.

"There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

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 engage-

ment 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.

The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

Problem cannabis use

Greater frequency of cannabis use increases the likelihood of developing Cannabia 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 posttraumatic 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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e have the right to twist ords? Why aren't case re- as evidence —especially regate them and cite them erns, as members of the bis Clinicians have done	search Society conference, Asilomar, CA. overlooked a paper based on N-of-1 trials published in <i>Anaesthesia (2004):</i> "Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies" by William Notcutt, MD and colleagues at the James Paget Hospital	\mathbb{A}	
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Clinicians' Evidence from previous page

findings in our A Tashkin's findings published in Can markers in Octobe

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Whoever wrote gorithm was impo dence' unsupporte Capital-S Science the meaning of wo ports recognized a when doctors aggr to document patte Society of Cannal over the years?

What is know impacts of cannabis by doctors and patients far exceeds what has been published in the journals sanctified by pubmed.

Over the years I've heard many a physician or researcher say, "The science shows..." or, "We now know..." in a reverent but forceful tone that implies "Take this as gospel truth."

What is known about the health impacts of cannabis by doctors and patients far exceeds what has been published in the journals sanctified by pubmed. The NASEM Report doesn't discredit the clinicians' findings -- it pretends they don't exist. Somehow the NASEM literature search

In science, "fact" can only mean "confirmed to such a degree that it would be perverse to withhold provisional assent."

and CBD) towards regulatory approval in the UK. In an O'Shaughnessy's interview (WHAT ISSUE), Notcutt recommended N-of-1 studies as a method by which US cannabis clinicians could compile data.

In an N-of-1 study, the patient serves as his or her own control. A given product or dose is tried for, say, a week, and a pain scale or other measure used to record effects. The number N of patients involved in each study is one, hence the name. Clinician can document patterns by aggregating the data from patients' N-of-1 trials

Did the NASEM search of the literature overlook studies other than Notcutt's in which cannabis was evaluated by N-of-1 trials? We'll never know. Maybe an algorithm was created -unbeknownst to McCormick and the NAS Report authors-that excluded N-of-1 trials as inherently low-quality evidence. Did an invisible valve get turned?

FRONTISPIECE OF MECHOULAM'S COMPENDIUM OF the relevant literature published in 1973.

Why devalue case reports?

In 1973 the great Israeli pharmacologist Raphael Mechoulam published a collection of papers on marijuana that included case reports from physicians. In the preface he urged his laboratory-based colleagues to respect clinical evidence:

"Clinical publications differ from laboratory ones: the latter are experimental, the former are frequently just observational This dichotomy is clearly reflected in the last chapter. Most of the papers cited describe 'cases' rather than 'experiments.' Hence the conclusions drawn may not be accepted as readily by the reader as those of the previous chapters. I believe, however, that in a field so full of contradictions and heated debate the material has been

nis own case report on a woman who used marijuana instead of alcohol to relax in social settings.

presented objectively ... "

Mechoulam understood and acknowledged that the value of case reports depended on the clinicians' objectivity. Contrast his approach to that of the NASEM Report authors, who dismissed all case reports as inherently untrustworthy.

Mechoulam's point of view is inherently democratic. He ended his introduction by quoting Gerald Le Dain, head of the Canadian Royal Commission on the Non-Medical 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

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-Stephen Jay Gould

Clinicians ignored from previous page

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 adverse side-effects.

For a few years, he was the only doctor known to readily issue approvals for lessthan-grave conditions such as chronic pain and depression. As other doctors began specializing in treating cannabis users, Mikuriya organized them into 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 paper "Cannabis as a First-Line Treatment for Childhood Mental Disorders," is a single case report. "Cannabis as a Substitute for Alcohol" is based on 92 case histories. 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).

The major findings have been confirmed by other studies over the years and this process will undoubtedly continue as the federal stranglehold on research weakens.

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

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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 Three who respected clinical evidence



GEOFFREY GUY, RAPHAEL MECHOULAM AND TOD MIKURIYA at the 1999 International Cannabinoid Research Society meeting in Acapulco. Guy's GW Phamaceuticals funded Notcutt's study based on N-of-1 trials. PHOTO BY FRED GARDNER

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 reported 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 NASEM decision to ignore cannabis clinicians' case reports is a form of blacklisting. The findings of cannabis clinicians have been barred from "the literature." The

disorder, particularly among regular or

• The development of any type of anxiety

· Increased symptoms of anxiety (near

· Increased severity of posttraumatic

"There is no evidence to support or refute

a statistical association between cannabis

• Changes in the course or symptoms of

stress disorder symptoms among individu-

als with posttraumatic stress disorder.

disorder, except social anxiety disorder.

daily users.

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daily cannabis use).

"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 supercedes workaday English.

A real scientist

The Israeli filmmaker Zach Klein followed his excellent Mechoulam biopic,

"The Scientist," with a documentary about cannabis as a treatment for autism.

Klein sent us a frame from the new project (see photo below) with a fact-checking note:

"I'm editing my documentary about autism (and cannabis) and I think that Mechoulam is looking at O'Shaughnessy's. Picture is attached. Did you publish something about the subject?"

Yes, we responded. The page that Mechoulam is looking at is from our Summer 2009 issue. It contained two case reports by Philip Denney, MD.

A colleague of Mechoulam's had evidently put the page in an envelope and mailed it to him in Israel, and Mechoulam had filed it for future reference. Which goes to show that the real scientist takes seriously material that elitists dismiss as "mere anecdotal evidence."

A Brief Report of Two Cases **Cannabis Treatment in Childhood Autism**

By Philip A. Denney, MD four being reported to the police or Child Protective Semicor

B.T. B.T. is an 11-year-old male, product

B.T. is an 11-year-old male, product of a accural-term pregnaccy and birth. Behavioral problems began at age 10 motths characterized by progressive via-lence and aggressiveness. At age 15 months, a diagnosis of Pervasive Devel-

By Philip A. D Autism Spectrum Disorder is an in-creasingly recognized behavioral illness of childhood characterized by develop-anenal delay, other profound. Many chil-dren diagansed as autistic are severely disabled and present major challenges to families, physicians, and edskarores. Vis-lent behavior directed at stell and others is a particularly difficult symptom. Cur-cent treatment modulines include fam-ly e ducation, behavior modification, and

sisted

and socialization.

His reachers have noted major improve-ments in learning and socialization, these positive changes have persisted for more than a year, while the dose of cannabis

has remained stable. The parents report no adverse effects of cannabis use, but

lence and aggressiveness. At age 15 months, a diagnosis of Pervasive Devel-opmental Delay was made. At age 17 mooths a diagnosis of Autism Spectrum Disorder was made. Despite aggressive intervention and multiple psychotropic Is a particularly difficult symptom. Cur-rent treatment modulities include fami-ily education, behavior modification, special education services, a wide vari-ety of psychotropic medications and in-stitutionalization in some cases. I have recently evaluated two enables whose families have decided to use ean-abis in lies of standard medications for treatment of autism. They report dra-ratic improvements. E.S. is a nine-year-old indopted male. He is the product of an uncomplicated full temo programsy delivered by C-sec-tion. The avariant period was unremark-able. Severe behavioral problems were noial beginning at 20 months, ultimately leading to a diagnosis of Autism. Despite aggressive meatreer with be-havioral interventions and multiple medications including the atypical medications, severe violent behavior persisted. The family described multiple injuries to B.T. and his caregivers and the need for around-the-clock assistance. Violent behavior ultimately prevented any school attendance at all.

Complete elimination of violent behavior and a marked increase in affection and coop eration

Noting internet reports of success whit cannabis for Antism and concerned about the use of psychotropic media-nen for their son, the parcels decided to try cannabis. The nearits were dramatic: with complete elimination of vielent behavior and a marked interase in al-fection and cooperation. B.T. has been able to retram to scheol and is described as a "different child." He has been able to eliminate his prescribed medications completely. Mom administers small servings of combread made with can-nabis-infixed oil and administly decies any adverse effects. medications including the atypical ntipsychotics, severe behavior problems, especially violent behavior, per His teachers have noted major improvements in learning

Encouraged by internet reports and desperate for an alternative, the parents began using small amounts of canabis concentrate administered in yogurt. The results were immediate and dramatic, Violent outbursts became rate, self-stimulation stopped completely. The child became calmer and more focused. adverse Conclusion In summary, these two cases suggest a potentially significant therapeutic role for the cannabinoids in the treatment of Autism Spectrum Disorder. Its safety and

lack of toxicity may make cannabis an attractive alternative to psychotropic medications for many children. In addi-tion, study of the endocannabinoid system as it relates to Autism may lead to a better understanding of both



about cannabinoids. And that the strategy for containing the medical marijuana movement was going to be a stall in the name of Science (as Tod Mikuriya called it). No more Cheech & Chong jokes. The new soundbite is "More research is needed."

In January '97, McCaffrey announced that the Drug Czar's office was allocating \$1 million for an 18-month study of the medical potential of marijuana by the Institute of Medicine

"I don't think anyone wants to

use of marijuana or other cannabinoids for the actual treatment of epilepsy... Nausea and Vomiting Associated With Cancer Chemotherapy: The relative efficacy of cannabinoids versus these newer antiemetics have not been evaluated.... There are no controlled studies of marijuana in the AIDS wasting syndrome, nor have there been any systematic studies of the effects of marijuana on immunological status in HIV-infected patients." Et cetera, et cetera...

Mikuriya emphasized the advan-

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

depressive disorders.

• The development of post-traumatic stress disorder.

The NASEM Report in Context

In November, 1996, California voters legalized marijuana for medical use, passing Proposition 215 by a 56-44 margin. We, the people were telling the government (and the medical establishment) that marijuana isn't dangerous, it can even be helpful.

On Dec. 30 Drug Czar Barry McCaffrey, flanked by Attorney General Janet Reno, Health & Human Services Secretary Donna Shalala, and NIDA head Alan Leshner held a press conference to declare the Clinton Administration's opposition to medical marijuana. Reno warned that MDs who approved marijuana use by patients could lose their licenses. McCaffrey declared, "This isn't medicine, this is a Cheech and Chong show."

In the days that followed, McCaffrey's line changed. Somebody must have told him settle issues like this by plebiscite," said Varmus, calling instead for "a way to listen to experts on these topics."

On Jan. 30, 1997, Harold Varmus, director of the National Institutes of Health, announced a special conference to resolve "the public health dilemma" raised by the passage of Prop 215. "I don't think anyone wants to settle issues like this by plebiscite," said Varmus, calling instead for "a way to listen to experts on these topics."

Varmus assigned Alan Leshner, the director of the National Institute on Drug Abuse, to organize the conference posthaste. The experts convened February 19-20. They called for clinical trials in many areas:

"Evidence that marijuana relieves spasticity produced by multiple sclerosis and partial spinal cord injury is largely anecdotal... There is scant information on the

tages of vaporization to the IOM.

In December 1997 the Institute of Medicine investigators held a public hearing at UC Irvine and visited Bay Area cannabis clubs. At the Oakland CBC, Tod Mikuriya, MD, explained that the club's intake form defined illnesses according to conventional ICD-9 codes. He shared information about his patients' cannabis use patterns and the impact on their illnesses. He emphasized the advantages of vaporization over smoking.

The IOM report, released in March 1999-

• confirmed that marijuana has been effective in treating chronic pain, nausea from cancer chemotherapy, lack of appetite and wasting in AIDS patients.

• strongly advocated research into and development of cannabinoid drugs.

• debunked the notions that marijuana is

continued on next page

Epilepsy & Behavior publishes study showing Cannabis reduces seizure frequency, severity

The NASEM Report was quickly out-ofdate with respect to epilepsy, thanks to the publication in *Epilepsy & Behavior (May* 2017) of a paper by Drs. Dustin Sulak, Russell Saneto, and Bonni Goldstein, entitled "The current status of artisanal cannabis for the treatment of epilepsy in the United States."

Goldstein reported on 225 patients with intractable seizures seen at her practice in the Los Angeles area. Saneto reported on 47 patients seen at Seattle Children's Hospital. Sulak, who is based in Maine, contributed four detailed case studies. They aggregated their results:

"Of 272 combined patients from Washington State and California, 37 (14%) found cannabis ineffective at reducing seizures, 29 (15%) experienced a 1–25% reduction in seizures, 60 (18%) experienced a 26–50% reduction in seizures, 45 (17%) experienced a 51–75% reduction in seizures, 75 (28%) experienced a 76–99% reduction in seizures, and 26 (10%) experienced a complete clinical response.

Overall, adverse effects were mild and infrequent, and beneficial side effects such as increased alertness were reported. The majority of patients used cannabidiol (CBD)-enriched artisanal formulas, some with the addition of delta-9-tetrahydrocannabinol (THC) and tetrahydrocannabinolic acid (THCA)."

Most newsworthy —historic, actually is the fact that a peer-reviewed publication has acknowledged the validity of data compiled by cannabis clinicians. Goldstein and Sulak are each identified as running "a private cannabinoid medicine practice." Kudos to the editors at *Epilepsy & Behavior* who recognized their findings as worthy of inclusion in their journal! A wall has been breached —kind of like when the Baseball Hall of Fame enshrined the star players from the Negro Leagues at Cooperstown. Sulak, Saneto and Goldstein are our Satchell Paige, Buck Shaw and Josh Gibson.

From now on, when medical-establishment experts review the evidence on cannabis as a treatment for epilepsy, the paper



A peer-reviewed publication acknowledges the validity of data compiled by cannabis clinicians

by Sulak et al cannot be overlooked. It's part of "the literature." It has been "published." (The jargon is inherently elitist.)

Because Sulak, Goldstein, and Saneto are cannabinoid-medicine specialists who care for patients in ways that go beyond documenting seizure reduction, their paper provides extremely pertinent information not typically found in medical journals. Consider the following dense, poignant paragraph listing the "non-medical risks" that physicians must bear in mind when recommending a trial of cannabis to the parents of epileptic children:

"Availability of a consistent supply of the medication is frequently interrupted due to horticultural, manufacturing, and economic factors. Current market prices for artisanal cannabis preparations observed in Maine, California, and online range from 5 to 50 cents per milligram. Higher dosing ranges are financially unfeasible for many patients unless they grow and produce their own medicine, a complex process that presents many potential interruptions in treatment. Sudden loss of access to cannabinoids may result in rebound seizures. Hospital admissions present challenges, and patients or their guardians often must choose between interrupting cannabis treatment and violating hospital policies that forbid self-administration of medications, especially those with Schedule I status. In one of the sites (RPS), the hospital has families sign a waiver and allows them to administer home dosing of product, but does not provide storage. The potential for disruption of medical treatment or family structure related to child protective services and other legal agencies, even when the patient and medical provider operate within state laws, must also be carefully considered on a case-by-case basis."

The bottom line from Sulak et al:

"Overall, the safety profile of qualitycontrolled herbal cannabis preparations is likely equal or superior to most Anti-Epileptic Drugs... Herbal cannabis has remarkably low toxicity, even at high doses, and no lethal dose of cannabis has been described. Conversely, the morbidity of AEDs are the most common impediment to achieving full effective dosing due to multiple types of toxicity ranging from tiredness to memory problems and even death." —O'S News Service

The current status of the United States	artisanal cannabis for the treatment of epilepsy in
Dustin Sulak ^{a,*} , Russell San	eto ^b , Bonni Goldstein ^e
integr# Health, 170 US R. 1, Fabroach, ME 04 Seattle Children's Hospital/Chilensity of Work Canas-Centers, 19601 Honofleane Fliel Saire 4	105, United Status ingle ng 4600 Send Paine Way, NP, Sender, WA 96105, Tinited Strives 1460 Transdain, CA 40020, United States
ARTICLE INFO	ΑΒSTRΑCT
ntice Missery: iceewed 27 September 2016 icetted 16 December 2016 icetted 17 December 2015 valiable online more	The widespread patient use of artisenal cannabis preparations has preceded quality vehicletion of cannabis use to epilepsy. Neurologists and cannabinoid specialists are increasingly in a position to monitor and guide the use or herical cannabis in epilepsy patients. We report the retrospective data on efficacy and adverse effects of artisan cannabis in Patients with medically refractory epilepsy with mixed etiologies in Witchington State. California, an Maine Clinical considerations, including potential risks and henefits, challenges related to artisanal preparation.
icywands: Indianal Canabbis Canabhold pilopsy Canabholdi Canabhold	and consubincial dosing, are discussed. Results: Of 272 combined patients from Washington State and California, 37 (142) found cannabits ineffective a reducing sciences. 29 (155) experienced a 1–25% reduction in sciences 49 (134) experienced a 26–50% reduction in sciences. 45 (173) experienced a 51–25% reduction in sciences. 75 (265) experienced a 26–60% reduction is selarces, and 26 (10%) experienced a 51–25% reduction in sciences. 20 (134) constrained a 26–60% reduction in infrequent and benchical scie effects such as increased alerthese were reported. The majority optimate use cannabiditi (100)-emiched artisanal formulas, some with the addition of cleina-9-tradyrine analytical responses. doses <0.1 mg/kg/day biphesic dose-response effects, the use of THCA for science prevention, the use of TH for seizure response, and the synergy of ramebinistics and responses in artisanal preparations.

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Percent sei	izure reduction	n attributed	to the	addition	of artisanal	cannabis:	combined	data
from Wash	nington and Ca	alifornia.						

% Seizure reduction	California	Washington	Combined	Percent of total
0	27	10	37	14%
1-25	29	12	29	15%
26-50	25	23	60	18%
51-75	45	0	45	17%
76-99	75	0	75	28%
100	24	2	26	10%
Total	225	47	272	



delta-9-tetrahydrocannabinol acid (THCA)

Why THCA?

In "The Current Status of Artisanal Cannabis in the Treatment of Epilepsy in the United States," Dustin Sulak, DO summarizes a case involving a 10-yearold boy who was started on a THCA-rich extract. We asked why THCA instead of CBD?

Sulak replied that THCA is often easier to come by. Plus:

"When people respond to THCA they usually respond at a much lower dose than they do to CBD. As a result, the trial takes less time. When you start someone on lowdose CBD it can take several months to work them up to the effective dose. With THCA it seems to go much faster, and of course a lower dose is more affordable for the families. So in many cases I'm starting with THCA —especially when the problem only involves seizures. If there are cognitive or behavioral issues, pain, spasticity, or other symptoms, I start with CBD or THC.

Sulak et al acceptingly cite a paper reporting that a placebo effect influences the claim that cannabis reduces seizures. I have heard parents of epileptic children scoff — and have scoffed myself — at the notion of such a placebo effect. Sulak said it's probably real in some instances, a function of the parents' desperate hope for progress.

He added. "A mother told me this week her daughter's seizures were doing much better, down to three-four seizures per week. I looked at my notes from three months earlier and it was three to five seizures per week. While I believe that she may be doing much better in some global sense, and I have a tendency in general to believe my patients' statements as valid truth, if not a scientific finding, I don't think all reports of seizure improvement are always accurate."

ECB blood serum levels

It was surprising to read in Russell Saneto's report on 47 patients from Washington State, "We are able to validate the product our patients are taking by serum analysis of drug levels."

Testing blood-serum cannabinoid levels is not being done by California doctors or patients. Sulak explained that Saneto had been involved in the clinical trial at Seattle Children's Hospital of Epidiolex, and that a lab in Pennsylvania had developed a panel to measure (certain) cannabinoid levels. Sulak hopes to get his patients access to a lab that can measure cannabinoid levels in the blood.

NASEM Report from previous page

addictive and that its use leads to heroin and cocaine use.

• noted that marijuana has a lower potential for abuse than alcohol or tobacco, and is safer than many commonly used drugs.

• found no evidence of cannabis providing benefit in the treatment of seizures, migraines, glaucoma, Parkinson's and Huntington's disease. and many other ailments for which patients and doctors claimed it provides relief.

Mikuriya's input on vaporizing was ignored, as was his data on patients using cannabis as a "harm reduction" alternative to alcohol and hard drugs. He called the IOM report "an exercise in bureaucratic consensual unreality.

"But even with their pseudo-cautious and tunnel vision definitions," he noted, "they delivered a product that contradicted McCaffrey's prevarications. Medicinal use

of cannabis is not a Cheech and Chong show! Cannabis has medicinal utility!"

Table 1

Mikuriya was deeply disappointed that IOM Report ignored what doctors had learned about cannabis use from patients —the clinical evidence.

"The narrow definition of the 'science base' has been degraded," he wrote, "contaminated, and deprived of clinical experience for more than 60 years by academic science and medicine.

"The IOM conspicuously chooses to exclude or minimize therapeutic efficacy for a variety of chronic illnesses.

"Unwillingness to believe or trust numerous cannabis users is the worst aspect of the report and results in a lack of clinical information. Left out is the reason patients use cannabis in the first place —it works, and with minimal toxicity for chronic conditions.

"By failing to acknowledge the relative freedom from adverse effects (when cannabis is compared with 'conventional'medicines) the IOM perpetuates the false stereotype of a dangerous drug."

How far have we come in 20 years?

The researchers whose work informs the NASEM Report were no more receptive to input from cannabis clinicians than their IOM predecessors. But they've seen the clinicians employ a whole new class of medicines, and they want in on the action. They have begun asking: why should research funds keep going to the search for harm, when the search for benefit can be so much more rewarding?

The NASEM Report ends with a recommendation to "Address Research Barriers: "The Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda."

Bottom line: there is a growing cadre of researchers who want to study cannabis as medicine. They will undoubtedly get a share of the taxes generated by cannabis sales. They should also get funding from big-time extractors who want their medicines tested.